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1. Authors should discuss briefly the quality control methods used to ensure that the data are complete and accurate. A reliable procedure should be cited for ensuring that all patients entered on study are actually reported upon. If no such procedures are in place, their absence should be noted. Any procedures employed to ensure that assessment of major endpoints is reliable should be mentioned (eg, second-party review of responses) or their absence noted.

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9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

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* *From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1–3, 1985).

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Antiemetic Studies: A Methodological Discussion[1]

I. N. Olver,[2] Richard M. Simon,[3] and J. Aisner[2,*]

Methodological issues encountered in reviewing the antiemetic literature are discussed. Variables affecting antiemetic assessment include those relating to the patient, the emetic stimulus, and the differences in action of the antiemetic drugs. Study design questions including the desirability of randomization, double blinding, use of controls, and stratifications for factors such as previous exposure to chemotherapy and strength of the emetic stimulus are discussed. From a statistical viewpoint a parallel subject design with adequate sample size is recommended. The problems of standardizing the evaluation of nausea and vomiting are considered and simple ordinal scales grading severity are suggested. The patient's overall assessment of tolerance of therapy is of primary importance. [Cancer Treat Rep 70:555–563, 1986]

Nausea and vomiting is a significant and occasionally limiting side effect of cancer chemotherapy. Not only does it adversely affect the patient's quality of life while receiving treatment (1), but it can exacerbate tumor-related anorexia and malnutrition. Severe emesis may compromise the physician's ability to deliver adequate doses of potentially curable chemotherapy (2).

Standard antiemetics have proven to be of limited efficacy against chemotherapy-induced emesis. The introduction of highly emetogenic agents, such as cisplatin, streptozocin, and dacarbazine, as well as the increasing use of combination chemotherapy, have compounded the problem. In the 1980s, therefore, there has been a rapid proliferation of antiemetic clinical trials reported in the literature (3). This effort has resulted in significant progress in controlling chemotherapy-induced emesis. An example, as will be discussed later, is the successful use of metoclopramide to alleviate severe cisplatin-induced emesis. Unfortunately, however, the large investment of time and effort in this area has not always yielded the maximum benefit.

The greatest difficulty in assessing many of the oral reports, written papers, and abstracts of such trials is that the information generated and the ability to compare studies are limited by faults in study design, evaluation, or both. Study design varies from open-label pilot studies to randomized double-blind comparisons between agents occasionally using placebo controls. Furthermore, antiemetic drugs are frequently given in differing doses and schedules making comparisons and general statements difficult. Since the chemotherapeutic emetic stimulus is not uniform and the patient population is heterogeneous, some trials consider stratification while others do not. Despite the proliferation of reports of antiemetics, there is no standard approach to these studies, not even to the assessment of antiemetic efficacy. Methodologic issues are thus important, and while recognizing the positive advances that research in this field has already made in a short time, the purpose of this paper is to discuss antiemetic studies from a methodological standpoint in an attempt to define an optimal approach to these clinical trials.

VARIABLES AFFECTING ANTIEMETIC ASSESSMENT

In a study to assess the efficacy of an antiemetic agent against chemotherapy-induced emesis, the outcome will be influenced by many pretreatment variables. Heterogeneity of the patient variables, the emetic stimulus, and the methods of administration of the antiemetic must all be considered.

Patient Variables

The severity of nausea and vomiting elicited by the same chemotherapeutic stimulus will differ widely over various patient populations (table 1). Acute postchemotherapy emesis is most often studied, although for some patients delayed and persisting emesis is more of a prob-

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TABLE 1.—Patient characteristics affecting antiemetic response

Proven
Age
Sex
Prior exposure to chemotherapy
Prior use of antiemetics (eg, THC)
Postulated
Psychosocial factors
a. Stress
b. Depression
c. Family support
Physical factors
a. Curable/noncurable
b. Performance status
c. Weight loss/nutrition

lem. An additional issue is that of anticipatory nausea. This aspect has been comprehensively reviewed by Moher et al (4), particularly from an etiological standpoint.

A major factor modifying the emetic response is previous exposure to chemotherapy. Many investigators have noted that patients who have had severe nausea and vomiting with previous chemotherapy tend to have less response to new antiemetic agents than those not previously exposed to the emetogenic stimulus. One possible explanation is that some patients who vomited repeatedly after prior chemotherapy may develop pretreatment nausea and vomiting as a conditioned response in anticipation of further chemotherapy. This anticipatory nausea and vomiting may prove particularly refractory to antiemetics. This has been reported most frequently in patients who received strong emetogenic agents such as cisplatin (5). Other reasons for this disparity between chemotherapy-treated and untreated patients are not immediately apparent and may lie in a host of psychosocial factors. Previously untreated patients, therefore, may be expected to have a better response to antiemetics with less nausea and vomiting. Conversely, they should also be more prone to any placebo effect when beginning a new antiemetic study drug. It is, therefore, important that patients previously exposed and not exposed to chemotherapy be analyzed separately.

The possibility of intrapatient variability in antiemetic response between courses of chemotherapy must also be considered. In theory, changes in a patient's physical condition, dependent on response to chemotherapy, may affect tolerance to therapy and emetic effects in subsequent courses. Cocchetto et al (6) have suggested that in evaluating new antiemetics, patients should receive the antiemetic on several different occasions so that interpatient variability may be quantified. Such trials with multiple treatment episodes may, however, become difficult to analyze for efficacy, particularly when a crossover design is employed and where the possibility of interaction between treatment arms exists, as will be discussed. The information on variability in response could be more easily gained if responders to the antiemetic being studied continued to receive it in an unblinded fashion over several further courses, as a second phase to the study. Laszlo et al (7) in reporting results of an antiemetic study involving 120 patients receiving delta-9-tetrahydrocannabinol (THC) cited several cases to support their contention that in humans the emetic response is reproducible when identical chemotherapy is given to the same individual. This is part of their justification for conducting an "open label," that is, unblinded study using historical controls. Whether this reproducibility can be confirmed is questionable, considering the multiple factors other than chemotherapeutic stimulus which may modify the emetic response and may vary between courses.

Age is another patient characteristic that can affect response in specific antiemetic studies and may have other unrecognized impacts. For example, with THC the greatest efficacy was reported in studies among younger patients (8–10). Central nervous system toxicity was more of a problem in older patients. In contradistinction, in studies with high-dose metoclopramide, younger patients seemed more prone to the extrapyramidal dystonic reactions (11).

The setting in which the patient receives the chemotherapy, ie, either on an outpatient or an inpatient basis, may impact on antiemetic efficacy. Inpatients may be more tolerant of side effects (12), perhaps because of a feeling of greater security. Another important area of concern is the interplay of various psychosocial factors. Stress, depression, and social supports have all been shown to have dramatic impact on treatment acceptance, tolerance, and toxic effects. Furthermore, these all have implications on compliance and the expression of complaints (13,14). Psychosocial stressors, both acute events and chronic problems, have been shown to be associated with deleterious physical and mental outcomes, whereas mediating factors, particularly social supports, serve to protect the individual from the full negative impact of exposure to stressors (15). This entire area has been inadequately studied with respect to impact on the severity of emesis due to chemotherapy and the response to antiemetic therapy but probably plays an important role.

Variability in Emetic Stimulus

Different chemotherapy agents vary greatly in the frequency and duration of nausea and vomiting that they cause. Nausea and vomiting usually occurs as a result of afferent input into the reflexly activated vomiting center in the medulla. This input can be peripheral from the gastrointestinal tract via pathways such as the vagus nerve, central via the chemoreceptor trigger zone, or psychogenic from the cerebral cortex. The mechanisms by which chemotherapeutic agents induce emesis are ill-defined. Data from animal studies are conflicting but certainly suggest different or multiple sites of action. For example, in cats, visceral afferents from the upper abdomen are important in mechlorethamine-induced emesis, while cis-

platin would seem to act via the chemoreceptor trigger zone (16). Thus, it is clear that the efficacy of an antiemetic drug may vary among chemotherapeutic agents. Also, there are some drugs like cisplatin, dacarbazine, mechlorethamine, or streptozocin which are associated with a consistently high incidence of emesis, while other agents such as chlorambucil, bleomycin, and vinca alkaloids are unlikely to cause nausea and vomiting and other agents are intermediate in their association with nausea and vomiting.

Among the highly emetogenic drugs, dose of chemotherapy is a major factor in the severity of vomiting. In a study of the efficacy of high-dose dexamethasone in patients treated with cisplatin, multivariate logistic regression analysis revealed that cisplatin dosage was the only significant predictor of emesis (17).

Antiemetic efficacy is also influenced by the schedule of its use since chemotherapeutic agents produce differing onsets and durations of emesis (18). The course of nausea and vomiting after high-dose cyclophosphamide, for example, has been described as starting after 6 hours, peaking at 12 hours, and persisting for 24 hours (19). Other agents with high emetic potential like mechlorethamine, cisplatin, and dacarbazine have a more rapid onset of action of ½–6 hours (16). These factors must be considered in planning dosing and duration of antiemetic studies. Thus, one schedule is not applicable for all chemotherapy agents.

Finally, it should be established whether the chemotherapeutic agent is, in fact, the cause of emesis (2). The underlying disease, particularly gastrointestinal malignancies, presence of cerebral metastases, metabolic effects like hypercalcemia, or use of other drugs such as opiate analgesics may be responsible for exacerbating or prolonging nausea and vomiting. Psychological factors as exemplified by the development of anticipatory emesis also modify the emetic response to chemotherapy.

Variables Related to the Antiemetic Drugs

The antiemetic and toxic effects of an antiemetic drug are clearly influenced by its dosage, schedule, and route of administration. The findings of pharmacokinetics and toxicity (phase I) studies have not been adequately completed for many of the antiemetic drugs and thus efficacy studies are difficult to compare because differing doses and schedules are employed. In addition, the utilization of drugs on a given schedule may have an important impact and drugs given on a regular schedule would probably have better efficacy and be easier to assess than those ordered on an as-required basis. Examples from the recent literature best serve to illustrate these points.

A good model for drug development can be based on the experience with metoclopramide (20). Metoclopramide was a very attractive antiemetic in animal studies, having activity against both apomorphine- and copper sulfate-induced vomiting, which suggests both central and peripheral sites of action (21). Moertel and Reitemeier (22) found metoclopramide to be ineffective against chemotherapy-induced emesis when they used the 20 mg three times a day oral dose suggested for use in diabetic enteropathy. Little more would probably have been done had not interest been rekindled with the advent of the highly emetogenic drug cisplatin and the finding of efficacy of high-dose metoclopramide (3 mg/kg) in dogs. In humans, low-dose oral metoclopramide had been unsatisfactory against cisplatin-induced emesis (23–26). Gralla et al (27) then conducted a phase I study in patients, elevating the iv dose to 3 mg/kg. Good antiemetic activity against cisplatin was noted. A series of randomized comparison trials with standard agents followed. Furthermore, a serum concentration-response relationship for metoclopramide is being investigated (29).

Schedule and dosage may be important determinants of antiemetic efficacy. For example, in two studies showing less efficacy for high-dose metoclopramide, a single dose was used in one study (30) and a 4-hour schedule was used in the other (31). Dosing every 2 hours as defined in Gralla's phase I study has been the schedule used in several positive studies (1,28,32–34).

THC is an example of an agent with widely variable results in reported trials (12), for which pharmacokinetic problems profoundly affected the ability to evaluate its efficacy. Doses and schedules have varied. Formulation is also important because of erratic gastrointestinal absorption but rapid peak concentrations after smoking (35). Also, drug tolerance to THC may limit its prolonged use or efficacy in prior marijuana users (10). Attempts to correlate plasma concentrations with side effects and antiemetic efficacy have yielded conflicting results (36,37). These studies were too small to draw conclusions about optimal dosing schedules. For example, three of nine patients of Frytak et al (36) had serum THC concentrations approaching undetectable levels between peaks. This might have indicated the need to alter the dosing schedule, but since these patients were being treated for gastrointestinal malignancies which may have altered absorption, no conclusion can be drawn. Chang et al (37) studied only eight patients in a group receiving doxorubicin and cyclophosphamide and found lower levels and less efficacy for THC in comparison to previous patients treated with methotrexate. Larger studies with pharmacokinetics may have provided more information on dosing schedules or drug interactions with THC. Clearly, this lack of pharmacokinetic information hampers assessment of clinical efficacy and the ability to interpret the discrepant results of studies.

Little attention has been paid to pharmacokinetics in the increasing number of antiemetic studies using dexamethasone alone or in combination (18). Dosing schedules are variable and appear quite empirical.

Of more interest is the lack of a dose-finding study for the most commonly used antiemetic, prochlorperazine. Given orally at low dose it has been the "standard" to

which newer agents have been compared. Few data are available on higher dose iv usage, although there is encouraging efficacy in some early studies with acceptable toxicity at several times the standard dose (38-40). In view of the metoclopramide experience, investigation of the toxicity and efficacy of high-dose prochlorperazine would seem warranted.

Finally, when single-agent activity is defined, it is appropriate to investigate antiemetic combination drugs with different sites of action such as metoclopramide and dexamethasone (41) or lorazepam and prochlorperazine (42). Until the single-agent activity of a new drug is known, however, it is not appropriate to test it in combinations. Care must also be taken that multiple antiemetic drug combinations do not influence growth of the tumor or obfuscate the efficacy of the chemotherapy. For example, steroids in lymphomas, leukemias, or breast cancer may influence evaluation of the chemotherapy, interact with the chemotherapy, or both.

STUDY DESIGN

Having completed phase I and "open label" (ie, unblinded phase II) pilot studies of an antiemetic it then becomes necessary to assess efficacy in a larger patient population. The design of the necessary study must ensure that it clearly answers the question of efficacy in an efficient manner which can be easily compared to similar studies. There are several aspects of study design to consider.

Randomization and Stratification

The main strength of randomization is in distributing unknown prognostic determinants according to a known random distribution so that their effects can be allowed for in statistical significance tests (43). Historical control groups are particularly problematic for antiemetic studies due to the necessity for comparability in emetic stimulus and prospective response assessment. In non-crossover studies, to ensure equal distribution of known prognostic factors before measuring the independent variable, stratified randomization is often desirable (44). From the previous discussion, the two most important variables to be matched are: (*a*) naivety or prior exposure to chemotherapy; and (*b*) strength of emetic stimulus (in current studies stratification is usually high-dose cisplatin or less emetogenic chemotherapy).

Some studies only include previously untreated patients receiving the same emetic stimulus and avoid the need for stratification. Prior exposure to chemotherapy may affect antiemetic efficacy so much that separate analyses of the two kinds of patients are highly desirable. Hence, if both kinds of patients are eligible for the trial, it is important to include sufficient numbers of each type for separate analysis.

Other variables such as age, sex, and underlying disease should be recorded to allow for analysis. Randomization will usually balance these general factors if the studies are sufficiently large. Other drugs that patients take should also be recorded, since they may affect subsequent analysis.

Double Blind

A double-blind design is essential to ensure unbiased evaluation by the investigator and elimination of any effects due to suggestion or expectation on the part of the patient or investigator. This is particularly applicable to antiemetic studies, where many of the parameters are subjective both in patient response and with assessment of response. This is a situation where unintentional bias can easily occur. This can only be eliminated by having neither the patient nor the investigator know which medication the patient is receiving, ie, a blinded controlled study. Effective blinding, however, may be difficult to achieve. Seipp et al (45), during a placebo-controlled blinded trial of THC, found that both patients and nurses often could identify the antiemetic therapy received based on response and side effects. The use of an active placebo, with similar sedative side effects, may have alleviated this problem of transparency. It has also been found that patients have been strongly influenced by prior reading of possible adverse effects on the informed consent form (46).

Placebo Control

The paucity of measurable objective response criteria in antiemetic studies emphasizes the need for randomized placebo-controlled studies. This need is underlined by the observation of responses in the inert control arms of reported studies, due to either a placebo effect or just a reflection of the variability of the emetic effect of chemotherapeutic stimuli.

Ethical considerations dominate the decision as to whether use of an inert placebo is appropriate. If an effective antiemetic were available, it should be the standard against which new agents are assessed. For example, the use of high-dose metoclopramide as a control in studies of cisplatin-induced emesis could now be justified. Attempts to avoid placebo controls have encountered other difficulties. Lucas and Laszlo (47) used previously treated patients who had failed standard antiemetic therapy as their own historical controls in an unrandomized, unblinded study. This avoided using an inert placebo or ineffective standard-therapy arm but adopted the difficulties of bias in unblinded nonrandomized studies as well as introduced the problem of prior chemotherapy exposure. Sallan et al (9) demonstrated the unpredictability of historical controls when a significant number of historical nonresponders responded to the standard emetic control arm of a THC study.

Cross Over

There are two major trial designs used in antiemetic studies. In a parallel-subjects design, the patients are randomized to receive either the study drug or control over several courses of therapy and the two groups compared. In a cross over design the same patient receives both the study drug and the control in a random order over successive courses of therapy.

In antiemetic studies where assessment is subjective, it seems attractive to have the patient serve as his/her own control. Also, by avoiding interpatient variability and evaluating each patient receiving both treatments, one might hope to reduce the number of patients required for a trial. These reasons were cited in a broad review of advances in antiemetic therapy by Bakowski (48), where many good studies using this design are cited in discussing advances of antiemetic drugs. There are, however, problems in evaluating cross over studies and the Biometric and Epidemiologic Advisory Committee of the Food and Drug Administration has discouraged their use (49).

Using a two-period cross over design for comparing a control Treatment C to an experimental Treatment E, one-half of the patients are randomly assigned to receive Treatment C in the first period and Treatment E in the second period while the other half receives the treatments in the reverse order. A cross over trial is inappropriate if there is some possibility that the emetic stimulus or environment for patient care will differ between periods; if the antiemetics have effects that last more than a single period; or if there are to be many patients lost to the study after the first period (eg, > 5%). Even in the absence of these conditions, however, there are problems with the interpretability of cross over trials. These problems result from the fact that relative efficacy of the two treatments may be different in the second period than in the first. For example, the experimental treatment may not be as effective in the second period when administered to patients with anticipatory nausea and vomiting who received an ineffective control treatment in the first period. Alternatively, the difference in treatment efficacy may appear greater for the second period if subjective self-evaluations of the experimental treatment are more favorable when elicited in the second period from patients who experienced an ineffective control treatment than when elicited in the first period from a new patient. Other scenarios are also possible. Consequently, a statistically significant difference may be difficult to interpret in practical clinical terms. This problem is exacerbated by sample size considerations. If the sample size were determined under the assumption that relative treatment efficacy was the same for both periods, then there may be far too few patients to reliably compare treatments if this assumption were incorrect, and there would not be enough patients to evaluate this assumption or to ascertain the nature of the interaction.

Consequently, although the two-period cross over design may result in increased efficiency, it may also result in reduced efficiency and difficulty of interpretation. It is also artificial as a model of patient care, since it does not permit one to evaluate the durability of antiemetic effectiveness over multiple periods when the treatment is administered under normal circumstances.

Numerous modifications to the two-period cross over design have been proposed (50,51). These variations, however, either sacrifice the concept of using the patient as his/her own control or require that all patients be available for more than two periods. Cross over designs, when used, require specialized methods of analysis (52–54). Rerandomization of patients for multiple periods with analysis by period rather than by patient is not valid.

SAMPLE SIZE

The sample size of an antiemetic study is of critical importance. The study must be large enough so that there is sufficient statistical power to detect the smallest difference of clinical importance. Many antiemetic studies contain very few patients. In such circumstances, failure to achieve significant differences should not be interpreted as a negative result but rather as an indeterminate result due to inadequate numbers. Reporting confidence intervals rather than P values is almost always more informative because a confidence interval clarifies whether results are negative or indeterminate. Studies which attempt to establish that a new antiemetic is as effective as a standard while perhaps being less toxic require particularly large numbers of patients because small reductions in efficacy must generally be excluded (55).

It is important to specify the target sample size in the protocol to ensure that spuriously positive results do not result from multiple reanalyses of accumulating data. The probability of statistically significant ($P = 0.05$) results by chance alone can exceed 20% if interim analyses are performed every 6 months in a 4-year study (56). Consequently, termination of a trial before the target sample size is achieved because of apparent differences should only be done if the differences are much more extreme than a P value of 0.05. Reports of antiemetic trials, as well as other kinds of trials, should indicate the target sample size and describe the frequency of interim analyses.

EVALUATION OF EFFICACY

Perhaps the greatest difficulty lies in the definition of response to antiemetics, ie, their efficacy. There are no broadly accepted standards of response as found in tumor measurements. The wide variation in the measurement of nausea and vomiting and the grading of antiemetic efficacy makes individual studies difficult to compare.

Consideration of individual parameters for measurement will highlight the problems involved.

What To Measure

The aspects of vomiting which can be quantified are the number of episodes and the duration and volume of emesis. Counting vomiting episodes is objective and can be done by either patient or an observer. The main difficulties are with continuous or prolonged vomiting and retching which do not involve expulsion of stomach contents but are a similar and uncomfortable response to the emetic stimulus. Volume of emesis is a less useful measurement unless variables such as intake can be strictly controlled. The duration of observation should relate to the time course of vomiting expected for the emetic stimulus used so that inclusive at-risk periods can be recorded.

Nausea is a subjective sensation where patient self-assessment must be the primary measurement tool. An observer may indirectly rate nausea by rating general level of discomfort, vital signs, appetite, or oral intake after chemotherapy (57).

Potential and unexpected side effects of the antiemetic drug should also be assessed and recorded. Patients may be able to record the degree of sedation or be asked to report unusual effects like dysphoria or dystonic reactions.

Questions which might determine the occurrence of anticipatory nausea and vomiting (4) would add useful information. This would add extremely valuable information about antiemetic efficacy, since among these patients nausea may prove to be more resistant to antiemetic therapy.

Who Should Measure?

The ideal situation is to have both the patient and the observer assess and interpret the efficacy of an antiemetic. Assessments can then be compared to check accuracy and interpretation. This is important when antiemetics with sedative properties like lorazepam and THC may compromise the accuracy of the patient assessment. More importance is given to the patient's assessment of subjective sensations such as nausea. It is preferable and widely practiced that the same specially trained team make these assessments in the hospital. Special training and dedication are also needed for optimal evaluation of outpatient regimens.

Scales of Measurement

The multiplicity of rating scales used in antiemetic studies have been reviewed by Morrow (3). The most common is the numerical scale with anywhere from 2 to 10 points. More recently, visual analog scales have been used to measure subjective parameters such as nausea (42). The analog scale approach follows a wider use in the evaluation of the quality of life in cancer (58). Its reliability and validity in evaluating nausea have been assessed by a test/retest method and found acceptable (19).

One of the greatest needs in the area of antiemetic research is the adaptation of standards of measurement. Although it is difficult to dogmatically state which method is best, any method must be both simple and reproducible. Having a large number of evaluation points to score a subjective experience does not necessarily increase the quantitative accuracy of the assessment, nor does multiplying several variables together to arrive at a score. Each parameter should be assessed separately and patients must be able to score the symptoms easily and reproducibly. In studying lorazepam, Bishop et al (42) found that the patients experienced difficulty with the linear-analog scales. A simple ordinal scale with 3–4 points may have proved easier.

One promising attempt at developing a standardized assessment of nausea and vomiting is the Morrow Assessment of Nausea and Emesis (MANE) scale (3). The scale is as follows: *questions to assess*—(*a*) anticipatory nausea; (*b*) anticipatory vomiting; (*c*) posttreatment nausea; and (*d*) posttreatment vomiting; and *elements assessed*—(*a*) frequency [4-point scale (during or after every treatment to never)]; (*b*) duration (hours nausea or vomiting lasts); (*c*) severity [6-point scale (very mild to intolerable)]; and (*d*) time when nausea and vomiting worse [6-point scale (during treatment to 24 hours after treatment)]. The reported test-retest reliability of the MANE scale for patients reporting nausea and vomiting shows acceptable consistency, while validity is still being examined. Although this type of scale is certainly appropriate for subjective measurements such as nausea, direct quantitation, such as number of vomiting episodes, where appropriate, may be more easily compared from one study to the next. It would also be desirable to assess other parameters such as degree of sedation, anxiety, and toxic effects to correlate with antiemetic efficacy (42).

Overall Assessment

There is no standard manner of expressing overall efficacy. Again, there is a clear need for standardization of definitions. In measuring response of a tumor to antineoplastic therapy, the terms complete and partial response are reasonably well-defined (54). The concept of a partial response in assessing emesis, however, is arbitrary. Also, response implies change, although change in emetic response cannot usually be observed directly.

Since the aim of an antiemetic is to completely abolish nausea and vomiting, it is proper to report complete response rates. Other nomenclature, however, may be preferred. Lesser responses are most accurately reported as incidences of nausea and emesis over the trial period. A psychometric scale for nausea, graded as simply none, mild, moderate, or severe, could be used. Vomiting is probably best reported as number of episodes over the

TABLE 2.—Schema for antiemetic assessment

Nausea
Pretreatment
Posttreatment
Severity [4-point scale (none, mild, moderate, and severe)]
Duration (hrs)
Vomiting
No. of episodes
Pretreatment (0–2, 2–4, 24 hrs)
Other parameters and toxicity
Anxiety (4-point scale)
Sedation [none, mild, moderate, and severe (duration of sleep)]
Specific toxic effects
Benzodiazepines (amnesia)
Cannabinoids (dysphoric reactions)
Phenothiazines (dystonic reactions)
4-point scale (none, mild, moderate, and severe)
Response
Complete response (no nausea or vomiting)
Lesser response
State severity of nausea on 4-point scale
No. of vomiting episodes during study
Patient's overall assessment
4-point scale (very well to very poorly)
Comments
Patient report why antiemetic not tolerated

study time which should include pretreatment. The two arms of a randomized study could then be directly compared.

Antiemetic efficacy alone, however, is not the only end point, since many agents have side effects which may limit their use. Conversely, some side effects may be partly responsible for the antiemetic effect. Fetting et al (19) reported that 70% of a group of patients receiving high-dose cyclophosphamide indicated that sleeping palliated nausea and vomiting. Thus, the sedation reported with phenothiazines, cannabinoids, and benzodiazepines may be desirable.

An important global assessment that includes all of the variables in the patient's assessment of his or her tolerance to a drug and perception of how well the nausea and vomiting was controlled is summarized in table 2. Although a direct comparison between agents seems easier where a patient is his or her own control, these studies have so many confusing factors and concerns that efficacy and side effects data are clearest in prospectively randomized parallel studies.

CONCLUSION

There is a large and growing literature on antiemetics, some of which is confusing because of methodologic problems in the design and reporting of antiemetic studies. To facilitate the interpretation of published results and the design of new studies, the highlights of trial design have been considered here. Before conducting large studies, it is desirable that optimum dose schedule and route of administration be defined in a dose-seeking (phase I) study.

Patients should be selected or stratified according to naivety to chemotherapy and by the emetogenicity of the chemotherapy that they receive. The chemotherapy should be administered in a standardized fashion.

A randomized double-blind parallel subject design is best. A cross over design, although sometimes useful, is not generally recommended. Sample size calculations should be made to answer the parallel design question and to allow for the detection of anticipated differences of reasonable size.

Study evaluations should include anticipatory symptoms, posttreatment nausea and vomiting, and side effects due to the antiemetic. Parameters are best assessed separately with simple scales. A standardized system would be ideal and agreement on such a scale is of paramount importance. We suggest that the severity of pre- and post-treatment nausea be assessed by a simple 4-point scale (none, mild, moderate, and severe) and the study time. Other parameters such as anxiety can be measured using a 4-point scale. Sedation can be assessed by both an ordinal scale and recording the duration of sleep.

It is important to report complete response, reflecting the aim of the study. Lesser responses could be simply quantitated for comparison rather than arbitrarily assigned a response category.

Toxicity can also be graded on a 4-point scale. Sedation would apply to most studies but more specific toxic effects depend on the agents used.

Finally, an overall statement by the patient should balance beneficial with adverse effects. Since it is the patient's quality of life that we are attempting to preserve, this overall assessment must be regarded as the most important.

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Morbidity of Cranial Relapse in Small Cell Lung Cancer and the Impact of Radiation Therapy[1]

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Thirty-nine of 225 patients with small cell lung cancer developed brain metastases after the initiation of chemotherapy. Treatment with high-dose dexamethasone in all 39 patients and cranial irradiation in 32 patients resulted in a complete neurological recovery in only eight of 39 patients (20%). Twenty-one of 39 patients (53%) failed to derive lasting benefit from their palliative treatment. Thirteen of 24 patients with limited disease with cranial relapse had no clinical evidence of other distant metastases prior to death and in these patients the CNS disease was an important cause of morbidity. On the basis of this study, it appears that palliative treatment of overt cranial metastases is relatively unsuccessful and that patients with limited disease represent a group with much to gain from effective prophylactic cranial irradiation. [Cancer Treat Rep 70:565–570, 1986]

Cranial relapse occurs in 20%–25% of patients with small cell lung cancer (SCLC), with the cumulative risk rising to ⩾ 50% at 2 years (1,2). Prophylactic cranial irradiation (PCI) reduces the average frequency of cranial relapse from 22% to 6% but this has not been associated with a survival advantage in several randomized trials (3–8). Currently, drug resistance is the major determinant of survival in SCLC and arguments for the continued use of PCI focus on improvements in the quality of survival rather than its duration.

Arguments against the use of PCI include the effectiveness of radiotherapy delivered at the time of cranial relapse (9,10), the fact that only patients achieving complete remission are potentially eligible for cure with PCI, and the potential CNS morbidity in a proportion of long-term survivors (11–13). The objectives of this retrospective study are to: (*a*) evaluate the effectiveness of palliation for CNS metastases; and (*b*) identify patients at high risk of isolated CNS relapse, for whom PCI might be indicated.

PATIENTS AND METHODS

Between May 1979 and December 1983, 225 patients with SCLC were entered in three consecutive chemotherapy protocols which have been the subject of previous reports (14,15). The treatment details are shown in table 1. PCI was delivered to 28 patients selected for high-dose cyclophosphamide after complete or good partial response to four courses of induction therapy (14). This protocol resulted in a delay of 5 months from initial diagnosis to PCI being given. After full marrow recovery, these patients received a midplane dose of 20 Gy in five daily fractions by opposed lateral fields (8-MeV x-rays). Elective thoracic irradiation was given to selected patients who failed to achieve a complete radiological response of locoregional disease to chemotherapy and was delivered to tumor doses of 40–55 Gy in daily fractions of 2 Gy using megavoltage x-rays.

Patient characteristics are shown in table 2. All patients had a cytological or histological confirmation of SCLC. Evaluation included physical examination; full hematological and biochemical screens; posteroanterior chest radiograph; marrow examination; isotope scans of the liver, bone, and brain; and fiberoptic or rigid bronchoscopy. The extent of disease was classified as limited if the tumor was confined to one hemithorax, with or without bilateral hilar or mediastinal lymph node enlargement, and included ipsilateral supraclavicular lymph node involvement. Patients with involvement beyond these limits were classified as having extensive disease.

All patients with intracranial metastases, developing after initiation of therapy, were identified for detailed review. Patients presenting with cranial metastases were excluded on the basis that they could not contrib-

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TABLE 1.—Treatment protocols

Date	No. of patients	Drug schedule (4 courses)	PCI
May 1979–July 1980	61	Cyclophosphamide, 1 g/m^2 iv on Days 1 and 22; methotrexate, 30 mg/m^2 iv on Days 1 and 22; and lomustine, 80 mg/m^2 on Day 1; every 6 wks	—
Aug 1980–July 1981	47	Cyclophosphamide, 1 g/m^2 iv on Day 1; methotrexate, 30 mg/m^2 iv on Day 1; and vincristine, 1.4 mg/m^2 iv on Day 1; every 4 wks	—
Aug 1981–Dec 1983	117	Doxorubicin, 40 mg/m^2 iv on Day 1; vincristine, 1.4 mg/m^2 iv on Day 1; and etoposide, 100 mg/m^2 iv on Days 1–3; every 3 wks ± Cyclophosphamide, 7 g/m^2	— 28 patients after cyclophosphamide

ute directly to the debate concerning the value of PCI. Brain metastases were confirmed by computerized tomographic scan in all patients but two who had positive isotope brain scans.

The dominant symptoms and signs of CNS relapse were recorded and the patients were assigned retrospectively to one of four categories of neurological function (NF), according to the classification of Order et al (16) (table 3).

The response to palliative treatment at cranial relapse was regarded as complete if patients achieved and maintained NF Category I for the remainder of their lives. Patients achieving and maintaining NF Category II for the remainder of their lives were regarded as having a "useful" partial response, and other patients were regarded as nonresponders.

RESULTS

Fifty-two of 225 patients (23%) were identified with cranial metastases, of whom 39 (17%) presented after the initiation of therapy. The classification of these 39 patients by NF function at cranial relapse is shown in table 4.

The treatment of cranial relapse included high-dose dexamethasone in all 39 patients and cranial irradiation in 32 patients. Radiotherapy was delivered by opposed lateral fields using 8-MeV x-rays and daily schedules (table 5). The responses to palliative treatment are shown in table 6. A complete response occurred in eight of 39 patients (20%) and a useful partial response occurred in ten of 39 (27%). Thus, one-half of the patients failed to derive lasting benefit from their treatment, and only three of these 21 patients showed transient improvement in neurological status, lasting for 1, 2, and 7 months, respectively, the remainder having progressive intracranial disease.

There was a suggestion that patients receiving higher radiation dose schedules had a higher response rate, with six of seven responses among patients receiving > 40 Gy in 4 weeks compared to six of 16 responses among those receiving 20 Gy in 1 week or 30 Gy in 2 weeks. This may, however, reflect patient selection rather than a dose-response relationship, since no randomized dose allocation was used. No relationship was

TABLE 2.—Pretreatment characteristics

Characteristic	No. of patients
Total	225
Age (yrs)	
Median: 63	
Range: 34–77	
Sex	
Male	156
Female	69
Stage	
Limited disease	113
Extensive disease	112

TABLE 3.—Classification of NF*

Category No.	Definition
1	Intellectually and physically able to work; neurological findings minor or not present
2	Intellectually intact and physically able to be at home, although nursing care may be required; neurological findings present but not a major factor
3	Major neurological findings requiring hospitalization and medical care and supervision
4	Requires hospitalization and is in serious physical and neurological state

*From ref. 16.

TABLE 4.—NF at cranial relapse

NF category	No. of patients
1	4
2	18
3	13
4	4
Total	39

seen between severity of initial neurological deficit and response. Of the eight patients who achieved complete response to irradiation, three were initially NF Category 3, four were NF Category 2, and one was NF Category 1. The presence of systemic disease at the time of CNS relapse did not influence response, with six of 18 responders (33%) and seven of 21 nonresponders (33%) having disease outside the CNS at relapse.

Two-year actuarial survival data for all 225 patients by stage at presentation are shown in figure 1, with a median follow-up of > 3 years (range, 6 months to 5 years). The cumulative probability of cranial relapse rose to 45% at 15 months in patients not receiving PCI (fig 2). Cranial relapse occurred prior to death in five of 28 patients (18%) given PCI after high-dose cyclophosphamide therapy. Because of their selected nature, no meaningful comparison of cranial relapse-free survival can be made between groups receiving and not receiving PCI.

In the 39 patients treated for intracranial relapse, mean survival of the 18 patients achieving complete or partial response to treatment was 7.5 months (range, 1-28) and in nonresponders was 3 months (range, 6-11). Only three responders survived for > 1 year, with death occurring in these at 21, 22, and 28 months, respectively. In 12 of 15 patients with extensive disease (80%), cranial relapse was associated with recurrence at other metastatic sites, whereas this was the case in only 11 of 24 patients with limited disease (46%). In 13 of 24 patients with limited disease (54%), cranial relapse was associated with no evidence of other distant metastases prior to death, although locoregional recurrence was present in nine of 13 of these patients (table 7).

TABLE 5.—Radiation schedules at cranial relapse

Total dose (Gy)/ No. of fractions	No. of patients
20/5	8
30/10	8
35/15	9
$\geq$ 40/20	7
Total	32

TABLE 6.—Life-time response of patients to steroids ± cranial irradiation

Response	No. of patients (%)
Complete	8 (20)
Partial	10 (26)
None	21 (54)
Total	39 (100)

DISCUSSION

The results of this study suggest that patients with SCLC developing symptomatic cranial metastases have a 50% chance of useful neurological recovery lasting the remainder of their lives. Other retrospective studies have recorded different response data for the palliative treatment of brain metastases. For example, Nugent et al (9) reported the treatment outcome in 68 patients with clinical evidence of intracranial metastases from SCLC (9). Seventeen of 68 patients (25%) died before either institution or completion of radiotherapy. Of 51 patients who completed radiotherapy, 47 (92%) had partial or complete resolution of neurological signs and symptoms. Baglan and Marks (10) reported complete responses to radiotherapy lasting the duration of patients' lives in 25 of 39 patients (64%) and partial palliation in eight of 39 SCLC patients (21%) with symptomatic brain metastases. In a retrospective analysis by Cox et al (17), 15 of 40 patients (37.5%) with brain metastases from SCLC had complete clinical response to cranial irradiation, 15 of 40 (37.5%) had partial response, and ten of 40 (25%) had no change or progressive deterioration in neurological function (17).

The lower response rates reported in the current study may reflect differences in patient characteristics and response criteria. In this respect, relief of symptoms in patients with good neurological function is reportedly better than in patients with poor neurological function (10). The presenting symptoms and signs of patients in the current study compared with those of two previous reports are shown in table 8. A high proportion of patients with ataxia was recorded, of whom only two achieved a complete and lasting remission. This frequency of posterior cranial fossa lesions is com-

TABLE 7.—Association of cranial relapse with other distant metastases according to stage at presentation

Stage at presentation	Clinical evidence of other distant metastases prior to death		No. of patients
	No	Yes	
Limited disease	13	11	24
Extensive disease	3	12	15
Total	16	23	39

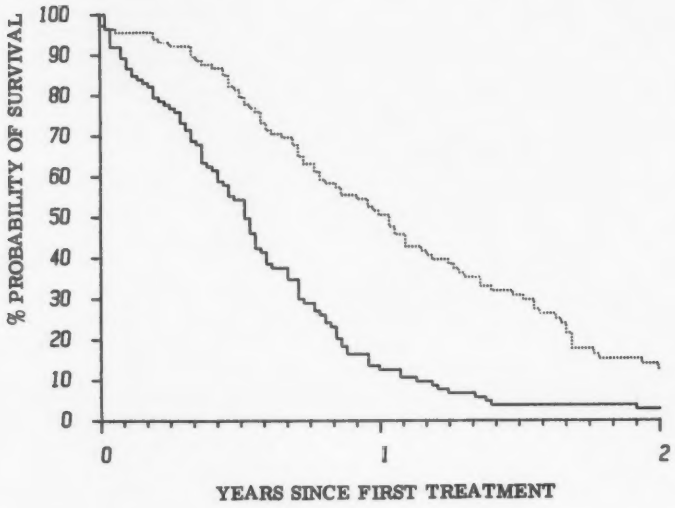

FIGURE 1.—Overall survival: limited vs extensive disease.

parable to the series of Hirsch et al (18), who reported clinical evidence of posterior cranial fossa deposits in 13 of 36 patients (36%) and autopsy evidence of deposits in the posterior cranial fossa in 19 of 36 patients (53%). Differences in the dominant symptoms and signs of cranial disease between studies may account for some of the differences in reported response rates. Other differences in response rates recorded after palliative cranial irradiation relate to different response criteria applied. The current study includes duration of response in the assessment of therapeutic effect, whereas some others report initial response rates only (9).

The failure of cranial irradiation to palliate a substantial proportion of patients with brain metastases is in part related to the radiosensitivity of SCLC. Intrathoracic SCLC usually shrinks rapidly after radiotherapy, but although SCLC may be more radiosensitive

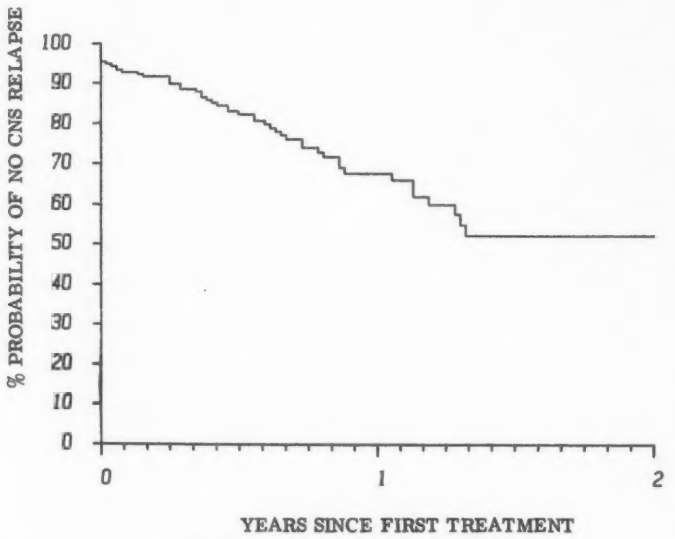

FIGURE 2.—CNS relapse-free survival: no PCI.

TABLE 8.—Summary of neurological symptoms and signs at cranial relapse

Symptoms/signs	Present study	Cox et al, 1980	Baglan and Marks, 1981
Ataxia	19	4	8
Hemiparesis	9	9	12
Visual defect	2	4	—
Confusion	9	11	11
Headache	5	11	13
Other	9	12	6
Total No. of symptoms/signs	53	51	50
Total No. of patients	39	35	39

than non-small cell lung cancer, it is not nearly as radiocurable as Hodgkin's disease or seminoma. The best radiation dose-response data for local control of intrathoracic SCLC suggest that doses close to the limits of normal tissue tolerance, ie, 50-60 Gy, are required for the eradication of macroscopic disease (19). In the brain, the effect of steroids on cerebral edema and rapid tumor shrinkage in response to radiotherapy may contribute to high rates of initial clinical response which may not be sustained if low or moderate radiation dose schedules are used. There is, however, no evidence to suggest that higher radiation doses would have improved the rate and duration of response, and prospective trials investigating the optimum dose schedule for the palliative treatment of brain metastases have failed to show a dose-response relationship (20-22).

In the prophylactic setting, low- or moderate-dose schedules appear to be reasonably effective against micrometastases. For example, doses in the range of 20 Gy in ten fractions to 40 Gy in 20 fractions reduced the rate of cranial relapse from an average of 22% to 6% in randomized trials of PCI (3-8). These observations do not necessarily mean that subclinical foci of SCLC are eradicated by these regimens, only that growth restraint lasted to death. In the current study, 20 Gy in 5 days given to 28 patients at the end of cytotoxic therapy failed to prevent cranial relapse in five (18%), suggesting that this dose may not be high enough. While the possibility of reseeding from other sites of disease cannot be excluded in these five patients, three of whom relapsed in the chest 5-6 months prior to cranial relapse and two of whom relapsed concurrently at multiple sites (23), consideration of the published data for tumor volume doubling times in SCLC suggests that the CNS relapse-free intervals observed after PCI in these patients are inconsistent with reseeding (24). An interesting finding in the present study was the absence of clinical evidence of other distant metastases prior to death in 13 of 24 patients (54%) presenting with limited disease. In a recent report the brain was the only identifiable site of SCLC relapse in five of 60 patients (8%) achieving complete response to chemotherapy (25). These data point to the possibility that a proportion of patients, particularly those presenting with limited disease and achieving complete response to initial therapy, may indeed have residual disease confined to the CNS.

In conclusion, the failure of current palliative radiotherapy schedules to confer lasting benefit in 50% of patients with brain metastases argues for the selective use of prophylactic radiotherapy for patients in whom the morbidity of CNS disease is likely to be a dominant feature of clinical relapse. On the basis of the current study, patients with limited disease represent a group with the most to gain from effective PCI. The optimum dose schedule and timing of PCI remain unclear.

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Neurotoxicity and Efficacy of Combined Vinca Alkaloids in Breast Cancer[1]

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We treated 17 patients with metastatic breast cancer with the four-drug combination of vincristine (0.5–1.0 mg), vinblastine (4 mg/m^2), doxorubicin (40 mg/m^2), and cyclophosphamide (400 mg/m^2). The two vinca alkaloids appeared to be synergistic in causing acute, reversible neurotoxicity, manifested primarily as diffuse pains involving one or more of jaws, limbs (particularly joints), chest, and abdomen. The response rate of 70% was no higher than that noted previously with a regimen identical to this one except for the exclusion of vincristine. Further studies of combined vinca alkaloids are not recommended in the treatment of breast cancer. [Cancer Treat Rep 70:571–573, 1986]

The vinca alkaloids vincristine and vinblastine are active in a number of different malignancies, including breast cancer (1). Despite having only very small differences in molecular structure (1), the drugs are not completely cross-resistant in human and other tumors (2–4), and dose-limiting toxic effects are quite dissimilar. Myelosuppression is the major dose-limiting toxic effect of vinblastine, while this complication is very unusual with vincristine. With vincristine, neurotoxicity is dose-limiting, while vinblastine usually causes neurotoxicity only at very high doses (1,5,6). We recently conducted a pilot study of the four-drug combination of vincristine, vinblastine, doxorubicin, and cyclophosphamide in the treatment of patients with metastatic breast cancer. We felt that it was reasonable to conduct such a study since we have demonstrated that the combination of vinblastine plus doxorubicin plus cyclophosphamide is active against breast cancer (7), since vincristine is also active against breast cancer (1), and since vincristine and vinblastine have different dose-limiting toxic effects (5,6) and are not completely cross-resistant (2–4).

METHODS

Seventeen female patients with breast cancer were entered in this study. All patients gave informed consent. None of the patients had had prior chemotherapy for metastatic disease. The ages ranged from 44 to 79 years (median, 63). Three patients had an Eastern Cooperative Oncology Group performance status of 0 (asymptomatic), six had a performance status of 1, four had a performance status of 2, three had a performance status of 3 (bedridden > 50% of the time, but not completely bedridden), and performance status was not recorded for one patient. Body surface areas ranged from 1.5 to 1.9 m^2 (median, 1.6).

All patients received vinblastine (4 mg/m^2), doxorubicin (40 mg/m^2), and cyclophosphamide (400 mg/m^2). We had previously found that these doses resulted in dose-limiting myelosuppression but little other toxicity (7). Specifically, we had noted no evidence of neurotoxicity. To this three-drug combination we added vincristine (0.5–1.0 mg). Each drug was administered iv in 50 ml of fluid over 10–15 minutes. Treatment courses were repeated at 3-week intervals, provided the patient had recovered from toxicity of the previous treatment course. Vinblastine, doxorubicin, and cyclophosphamide doses were reduced by 20% in some instances for granulocyte count nadirs < 500 μl and were escalated by 20% in some instances for granulocyte count nadirs > 1500/μl and platelet count nadirs > 125,000/μl. Prophylactic trimethoprim-sulfamethoxazole was given during periods of neutropenia. Dexamethasone, metoclopramide, and prochlorperazine were used as antinauseants. Doxorubicin was discontinued after a total cumulative dose of 450 mg/m^2. Four patients received tamoxifen (10 mg orally twice daily) in addition to the chemotherapy.

Blood cell counts were repeated at weekly intervals. Biochemistry profiles of renal and hepatic function were repeated prior to each course of treatment. In

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addition, patients were examined for evidence of response and toxicity prior to each course of treatment. Complete remission was defined as the complete disappearance of tumor and resolution of all symptoms. Partial remission was defined as a $\geq$ 50% reduction in tumor size or partial blastic healing of lytic bone lesions lasting $\geq$ 4 weeks. Stable disease was defined as tumor shrinkage of < 50% and tumor growth of < 25% for $\geq$ 8 weeks. Failure was defined as tumor growth of > 25% in < 8 weeks or the appearance of new lesions.

RESULTS

One patient failed to return for follow-up and thus was inevaluable for toxicity and response. Neurotoxicity developed in six of 16 (38%) evaluable patients, and three additional patients had symptoms that could possibly have been due to mild neurotoxicity. One patient had no neurotoxicity at vincristine doses of 0.5 and 0.7 mg, but did develop neurotoxicity at a dose of 1.0 mg. Definite neurotoxicity developed in none of six patients treated with 0.5 mg of vincristine, in one of three (33%) treated with 0.7 mg of vincristine, and in five of nine (56%) treated with 1.0 mg of vincristine per treatment course. In each case, the neurotoxicity developed during the first treatment course at that particular dose level. Body surface areas ranged from 1.5 to 1.8 m^2 (median, 1.55) in patients developing neurotoxicity and from 1.5 to 1.9 m^2 (median, 1.75) in those not developing neurotoxicity. Vincristine dose based on body surface area ranged from 0.39 to 0.67 mg/m^2 (median, 0.65) for patients developing neurotoxicity and from 0.28 to 0.67 mg/m^2 (median, 0.35) for patients not developing neurotoxicity.

Neurotoxicity consisted of severe constipation temporally related to treatment in one patient. The patient had not previously had constipation and was not taking narcotic analgesics. The severe constipation resolved after several days, and recurred with the following course of treatment, but did not recur subsequently when vincristine was discontinued.

Two patients developed severe jaw pain accompanied by diffuse aching pains and particularly severe pain in the wrists and ankles. In one patient, these pains were particularly severe at night while she was recumbent. Neither patient showed evidence of sensory loss, motor weakness, or joint swelling or erythema, and neither experienced paresthesias. In one of these two patients, carbamazepine was administered without benefit. Both patients experienced prompt relief with administration of a short course of prednisone (60 mg daily).

Two patients developed moderately severe pain in both arms shortly after receiving the treatment. This arm pain was accompanied by diffuse chest pain without electrocardiographic or other cardiac abnormalities in one patient and was accompanied by throat pain (without erythema or ulceration) and generalized weakness in the other patient. All symptoms resolved spontaneously over 7-10 days. One of these two patients received a subsequent course of treatment with a lower dose of vincristine (0.7 vs 1.0 mg) and had no recurrence of symptoms.

One patient developed abdominal pain, severe jaw pain, and mild paresthesias with her first course of treatment, but subsequently developed only transient mild paresthesias with re-treatment at the same drug doses.

Equivocal neurotoxicity consisted of insomnia and generalized weakness in one patient, insomnia and palpitations in a second patient, and severe insomnia and pain over the lateral aspect of the thighs in a third patient. The third patient also complained that when she closed her eyes her mind "raced" uncontrollably. The mind "racing" and insomnia but not the thigh pain recurred when she was re-treated without vincristine. She had received phenothiazine as an antiemetic and it it possible that this was the cause of her restlessness.

Other toxicity consisted of granulocytopenia (< 1000 cells/μl) in 65% of evaluable treatment courses, thrombocytopenia (< 100,000 cells/μl) in 1%, and combined granulocytopenia and thrombocytopenia in 3%. No nausea or vomiting occurred in 11% of evaluable courses, mild nausea without vomiting occurred in 51%, moderate nausea with vomiting occurred in 32%, and severe vomiting occurred in 6%. One of the patients with severe vomiting also experienced hematemesis. Eleven courses were accompanied by mild to moderate stomatitis, two were accompanied by the development of herpes zoster infections, and one was accompanied by the development of atrial fibrillation.

Three patients had no tumor evaluable for response and one patient failed to return for follow-up. Of the 13 evaluable patients, one (8%) achieved a complete remission, eight (62%) achieved partial remissions, three (23%) had stable disease, and one (8%) failed. Three of the four patients (75%) receiving tamoxifen responded compared to six of the nine patients (67%) not receiving tamoxifen. Neither the patient achieving complete remission nor the patient failing was receiving tamoxifen. Median duration of response from initiation of treatment was 23 months (range, 12-24) for patients receiving tamoxifen and 12 months (range, 2-23) for those not receiving tamoxifen. Median follow-up on all patients entered in the study has been 26 months (range, 2-39), and median survival has not yet been reached. Nine patients remain alive 24-39 months after initiation of treatment.

DISCUSSION

Many chemotherapy agents are capable of causing neurotoxicity (5,6,8), and for vincristine, neurotoxicity is dose-limiting (1,5,6,8). The usual recommended dose of vincristine is 1.4 mg/m^2 up to a maximum dose of

vincristine is 1.4 mg/m^2 up to a maximum dose of 2.0 mg (1). In practice, most adult patients are treated with a standard dose of 2.0 mg. Vincristine usually only causes neurotoxicity at very high doses. In our previous study of the combination of vincristine, doxorubicin, and cyclophosphamide using vincristine doses as high as 6 mg/m^2, we saw no evidence of neurotoxicity from the vincristine (7). The high incidence of acute neurotoxicity that we noted in this study of combined vincristine and vinblastine was somewhat surprising in light of the fact that we were using a maximum of only one-half the usual dose of vincristine and less than one-half the usual maximum dose of vinblastine (1). At the usual maximum doses of these drugs, one would ordinarily expect only a small proportion of the patients to develop such severe acute neurotoxicity with vincristine or vinblastine (1,5,6,8). In addition, the joint pain noted in two of our patients was unusual. Joint pain is not a common manifestation of vinca alkaloid neurotoxicity (1,5,6,8). Overall, it appears that the two drugs could possibly be synergistic in causing acute neurotoxicity. Our data strongly suggest that the neurotoxicity is related to the vincristine dose, but we have insufficient data to determine the relationship to the vinblastine dose.

In a previous report of concurrently combined weekly vincristine and vinblastine (9), it was stated that no aggravation of neuropathy was apparent; however, moderate to severe neuropathy was common and occurred at cumulative vincristine doses as low as 0.01 mg/kg (approximately 0.4 mg/m^2), with the median cumulative vincristine dose associated with symptomatic neuropathy being 0.036 mg/kg (approximately 1.5 mg/m^2). One would not ordinarily anticipate much neuropathy at such a low cumulative vincristine dose. In a subsequent study of vincristine and vinblastine given together daily for a 3-day course repeated every 3 weeks, symptomatic neuropathy was again common, and occurred at a median cumulative vincristine dose equivalent to 1.5 mg/m^2 (10). Symptoms of neurotoxicity were not described in sufficient detail in these reports to permit comparison with our experience; however, we feel that the data presented in these two reports support our contention of augmented neurotoxicity despite the authors' assertion that neurotoxicity was not increased.

Toxicity other than neurotoxicity appeared to be very similar to that seen with our previous study of vinblastine, doxorubicin, and cyclophosphamide without vincristine (7). The response rate was also very similar to that seen in our previous study. While too few patients were treated to permit an accurate estimation of the true response rate, it is highly unlikely that the addition of vincristine has added substantially to the efficacy of our previous regimen. The response rate in our previous study was 72% (including 9% complete remissions) compared to 70% in this study (including 8% complete remissions).

In summary, combining vincristine with vinblastine, doxorubicin, and cyclophosphamide in the treatment of breast cancer appears to result in synergistic acute, reversible neurotoxicity, but does not appear to markedly alter efficacy. We do not recommend further studies of this four-drug combination in breast cancer.

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Iv Infusion of Opioids for Cancer Pain: Clinical Review and Guidelines for Use[1,2]

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To assess the safety, efficacy, and use of continuous iv infusion (CI) of opioids for cancer pain, we reviewed the clinical experience of 36 patients who received 46 CIs. CI was always preceded by a period of repetitive dosing of opioids. Morphine was used in 36 CIs, methadone in four, hydromorphone in four, oxymorphone in one, and levorphanol in one. Mean doses during CI were the morphine equivalent of 17 mg/hour (range, 0.7–100) at the start, 69 mg/hour (range, 4–480) at the maximum, and 52 mg/hour (range, 1–480) at termination. Pain relief was acceptable during 28 CIs, unacceptable during 17, and unknown during one. There were few toxic effects other than sedation. Twenty-five patients died, 12 resumed im or oral opioids, six continued CI with a different opioid (yielding analgesia in two), and outcome was undetermined in three. This review suggests that (*a*) CI is safe, (*b*) analgesia may require rapid escalation of infusion rates, (*c*) patient response varies and lack of acceptable analgesia may occur in up to one-third, (*d*) ineffective CI with one drug may be followed by success with another, (*e*) CI should be preceded by a period of repetitive iv boluses with the same drug, and (*f*) guidelines can be developed which incorporate pharmacokinetic principles. [Cancer Treat Rep 70:575–581, 1986]

Continuous iv infusion (CI) of opioid medications has been reported to be an effective therapy for postoperative pain (1–3) and cancer pain in patients inadequately treated by analgesics given by alternate routes (4–9). For cancer patients, this method had been most commonly used for patients with advanced disease prior to death. A survey of 210 terminally ill patients treated during a 2-year period revealed that 13% received a morphine CI before death (9).

There has been little published documentation of the safety and efficacy of CI in the treatment of cancer pain despite its widespread and largely empiric use. Guidelines for patient selection and choice of drug and dose have not been discussed. Pharmacokinetic factors, which have received limited attention in postoperative pain management (2,10), have not been evaluated in patients with chronic cancer pain and the development of tolerance has not been addressed.

We reviewed 46 infusions in 36 patients with cancer pain to determine the safety and efficacy of this approach and to develop guidelines for its clinical use in cancer pain management.

MATERIALS AND METHODS

We retrospectively examined the charts of 36 patients who were evaluated by the Pain Service of Memorial Sloan-Kettering Cancer Center during the 3-year period of January 1981 to December 1983 and who received an opioid CI for the management of either acute or chronic cancer-related pain. Forty-six infusions were reviewed, comprising approximately 3% of Pain Service consultations during this period. Infusions were managed jointly by Pain Service personnel and the oncology staff involved with the case. For each infusion, patient characteristics, prior opioid exposure, duration of infusion and opioid drugs used, pain relief, and side effects were recorded. When indicated, the rationale for the use of CI was noted.

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RESULTS

Patient Characteristics

The median age of the 36 patients was 42 years (range, 1.5-67). All patients had cancer and all except one had known active disease. Pain was related to tumor invasion in 32 patients, to the effects of cancer therapy in three, and was unrelated to the cancer or its therapy in one. Thirty-one patients had chronic pain; 21 were receiving chemotherapy and/or radiotherapy at the time of CI, while ten were being offered only supportive care. Five patients had acute postoperative pain. All patients had continuous pain, which was focal in 20 patients, multifocal in seven, and diffuse in nine. At the start of 39 infusions, the patients' estimated Karnofsky score was ≤ 50; it was ≤ 20 in six infusions and could not be determined in one.

Prior Opioid Exposure

Prior opioid intake varied considerably among patients. The duration was reported for a minority of patients and ranged from 3 weeks to 4 years. In the 2 weeks prior to CI, 12 patients were prescribed a single opioid drug, while 24 consumed two or more; of these, three took four and one used five different drugs. The quantity of opioid medication expressed in im morphine equivalents (11) (table 1) taken in the 24 hours prior to each CI ranged from approximately 40 to 11,000 mg. For those patients switched from one CI to another, this amount was calculated as the total 24-hour iv dose prior to the change, again expressed in morphine equivalents. Fourteen patients received < 100 mg, 22 received 100-500 mg, and ten received > 500 mg. This last group included three patients who received approximately 1500, 6000, and 11,000 mg, respectively, during the day before CI and one who was given 100 mg of intrathecal morphine concurrently.

TABLE 1.—Relative potencies (equianalgesic doses) of opioid analgesics*

	Im (mg)	Oral (mg)
Oxymorphone	1	6
Hydromorphone	1.5	7.5
Levorphanol	2	4
Methadone	10	20
Morphine	10	60 (20-30)†
Oxycodone	15	30
Meperidine	75	300
Codeine	130	200

*From ref 11.

†Im:oral relative potency for morphine following single-dose studies is 1:6. Following repetitive dosing, im:oral has been clinically defined as 1:2-3. We recommend using this 1:2-3 ratio in calculating a starting dose in the chronic cancer pain patient.

Infusion Drugs, Dosage, and Duration (table 2)

Morphine was used in 36 infusions, methadone in four, hydromorphone in four, oxymorphone in one, and levorphanol in one. The dose ranges for these drugs are shown in table 2. The dose required during the infusion varied widely and was dependent on several factors, including the patient's prior opioid experience, the progression of disease, and the level of pain. Expressed in morphine equivalents, the mean starting dose was 17 mg/hour (range, 0.7-100), the mean maximum infusion rate was 69 mg/hour (range, 4-480), and the mean rate at infusion termination was 52 mg/hour (range, 1-480). The maximum rate was greater than that at the start during 42 infusions; doses at the time of termination of the infusion were lower than the maximum dose in 17. The duration of CI varied from 1 to 45 days. Five patients were treated for < 3 days, 13 for 4-6 days, 13 for 7-13 days, seven for 14-21 days, three for 22-29 days, two for 30-37 days, and three for 38-45 days.

Concurrent Medications (table 2)

Other medications, including opioid analgesics, were frequently administered during CI. Single iv bolus injections of opioids were used intermittently with 20 infusions; oral and rectal opioids were given in nine and intrathecal morphine was given in one. Sedative/hypnotic drugs were prescribed in 19 infusions, neuroleptics in 19, tricyclic antidepressants in 13, corticosteroids in ten, anticonvulsants in six, antihistamines in nine, and acetaminophen in nine.

TABLE 2.—Drugs used during CI (N = 46)

	No. of infusions	Dose range (mg/hr)
Infusion drug		
Morphine	36	0.7-256
Methadone	4	3-40
Hydromorphone	4	4-60
Oxymorphone	1	4-7
Levorphanol	1	10-96
Additional drugs		
Sedative/hypnotics	19	
Neuroleptics	19	
Tricyclic antidepressants	13	
Corticosteroids	10	
Acetaminophen	9	
Anticonvulsants	6	
Antihistamines	9	
Epidural bupivicaine	4	
Additional opioids		
Iv	20	
Oral/rectal	9	
Intrathecal	1	

Rationale for Iv Route and for CI

The rationale for choosing either the iv route of administration or CI was recorded from physician notes if stated directly or was inferred from the general clinical situation and comments made in both physician and nursing notes. The choice of CI was often unrelated to the decision to use the iv route of administration. In 16 patients, iv administration was chosen when all routes were available, but pain was severe and rapid analgesia was needed. In six patients, most of them children, the oral route was not tolerated and injections were not desired. Neither oral administration nor injections were tolerated in four patients. These occurred in patients with bleeding diathesis or diminished muscle mass who developed intractable vomiting, bowel obstruction, or malabsorption. In three patients, the iv route was used to maintain analgesia when other routes were temporarily unavailable during a procedure. Finally, no explanation for an iv route of administration was offered in five patients and no repetitive iv doses were given prior to CI in 12.

The indications for CI described in patients' charts included the following. Prominent bolus effects occurred in 20 patients. This was characterized by the onset of side effects, most often sedation, in the first hour after an iv dose and/or by pain breakthrough immediately before the next iv bolus was administered. A desire for rapid titration of analgesia was described in seven patients. As noted, this indication was reported both by physicians who chose CI and those who decided upon an iv route of administration. Ease of nursing was a rationale in one patient who required iv injections more frequently than every 2 hours. In one patient, CI was motivated by a desire for sedation, while concern over the size of individual doses given by iv bolus was noted in another. In 16 patients, no explanation was offered, but it was implied that CI was chosen because analgesia was needed and patients were terminally ill. Such a view is apparent in the number of patients who died while receiving CI.

Outcome of CI

Pain relief was considered to be acceptable if the patient remained awake and coherent and analgesia was reported to be adequate in either physician's or nurse's notes during consecutive days after CI was begun. Pain relief was attained in 28 infusions and was inadequate in 17. The efficacy of CI in the 18-month-old patient could not be assessed by these criteria. In patients with inadequate pain relief, doses were increased until there were limiting side effects. In six of these 17 unsuccessful infusions, persistent pain and/or intolerable side effects led to a trial of CI with an alternative opioid. Two of these replacement CIs produced analgesia not achieved by the original infusion and two yielded continued analgesia with significantly fewer side effects.

Three dosing patterns during CI could be discerned and are illustrated graphically by the patients shown in figure 1. Patient 1 was a 45-year-old woman with a lumbosacral plexopathy due to cervical cancer who had adequate analgesia on CI but required a rapid escalation of dose to maintain it. Patient 2 was a 77-year-old woman with bony metastases from lung cancer who had excellent analgesia on CI for 16 days and required almost no increase in dose. Patient 3 was a 38-year-old woman, also with a lumbosacral plexopathy due to cervical cancer, who never achieved analgesia despite continual dose escalation. In this patient, doses stabilized only when dexamethasone was added to the infusion. All patients receiving CI conformed to one of these patterns during the course of the infusion.

Side effects associated with CI are shown in table 3. Since CI was preceded by repetitive iv boluses in 34 of 46 infusions, side effects prior to CI were compared with those occurring 2–3 days after it was begun. Progressive sedation occurred during 21 infusions, while a new onset of confusion was noted in nine, multifocal myoclonus in three, nausea in two, and constipation in two. Respiratory depression, which was easily reversed with iv naloxone, occurred in one patient who was concurrently receiving intrathecal morphine. Although the assessment of side effects was complicated by the poor clinical status of many of the patients and the multiple therapies they were receiving, the use of CI did not appear to carry a significant risk of toxicity.

CI was maintained until the death of the patient in 25 patients. In 15 of these patients, the final infusion rate was lower than the maximum attained during the CI, although usually only a modest tapering of dose occurred prior to the death of the patient. Twelve infusions terminated with a return to im or oral dosing of opioid medications; six ended with a trial of an alternative CI and outcome was not determined in three.

DISCUSSION

CI is a safe method of opioid administration which can effectively control cancer pain in two-thirds of the

TABLE 3.—Side effects during continuous opioid infusions*

	Total during CI	Beginning or progressing during CI
Sedation	32	21
Confusion	19	9
Nausea/vomiting	17	2
Constipation	13	3
Myoclonus	3	3
Dizziness	1	0
Respiratory depression	1	1
None	14	—

* Values = No. of patients.

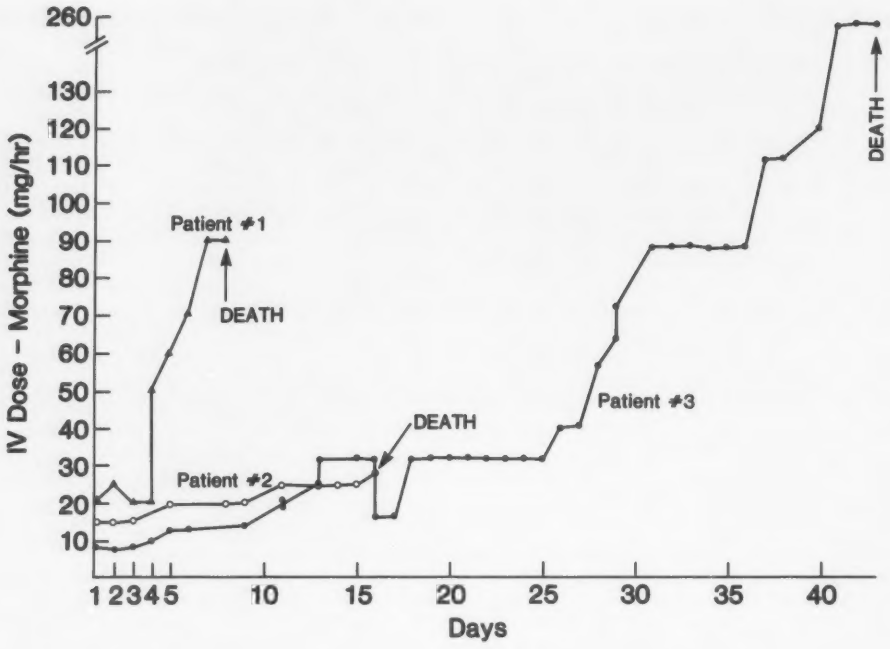

FIGURE 1.—Variability among patients in dose escalation during CI. Patient 1 maintained analgesia throughout CI but required rapid escalation of infusion rate, to a maximum of 150 mg/hr of morphine. Patient 2 also had excellent analgesia for the duration of the CI, requiring almost no increase in infusion rate. Patient 3 never achieved analgesia from the CI, despite rapid escalation of infusion rates. Infusion rates stabilized in this patient only when dexamethasone was added to the analgesic regimen (1st plateau) and after its dosage was doubled (2nd plateau).

patients to whom it is prescribed. In all patients, the application of this technique should be preceded by a firm indication for its use; once prescribed, the choice of drug must be individualized and doses titrated against the level of pain, desired pain relief, and incidence of side effects. Based on the present survey, published experience, and pharmacokinetic principles, both indications for CI and guidelines for use can be defined.

It is apparent from this review that indications for an iv route of administration and those for CI can be distinguished. Thirty-four infusions in this series followed a trial of repetitive iv administration. CI requires an extra step in preparation, with the attendant cost of a specialized drug delivery system and risk of contamination, and has been associated with the development of phlebitis (7) and accidental overdose (3). A patient who requires an iv route of administration and who achieves adequate analgesia with repetitive doses would gain little and may be exposed to a small additional risk by its use. Until controlled studies are done which compare these alternative methods in chronic cancer pain, it is advisable to institute a trial of repetitive iv dosing prior to CI in most patients. This practice also permits an estimate of drug requirement which may be useful in computing the starting dose of CI.

CI should be considered as a method of pain control in the following situations. (*a*) It can be used to obviate the occurrence of bolus effects. As plasma levels ascend rapidly, the bolus effect may result in unacceptable side effects soon after a dose is given. In this setting, CI can often provide smooth and continuous analgesia as the steady-state plasma level presumably stabilizes at a point between the peak and trough levels. (*b*) It can provide rapid titration of analgesia. Since the rate of rise in plasma drug concentration depends on the infusion rate in CI and the size and frequency of the bolus in repetitive dosing, either may provide a more prompt analgesia. This is not, therefore, a strong indication for CI. (*c*) It can facilitate nursing care. This is a legitimate concern when patients require doses every 2 hours or more or when regulations prevent the nurse from administering iv opioids.

Three other indications for CI use, noted in this review, have limited validity. A desire for sedation, described by one physician prior to CI, can be achieved with either repetitive dosing or CI and is probably best obtained with a nonopioid, sedative/hypnotic drug. Con-

cern about the size of individual doses, also mentioned by one physician, represents only the degree of tolerance and, in the absence of significant bolus effects, is without relevance. As described above, hourly doses during CI can also become enormous. Finally, many infusions were begun with the implicit explanation that the patient was terminally ill. In the presence of adequate analgesia with repetitive dosing, a switch to CI in the dying patient would of course be unnecessary. With persistent pain, CI becomes appropriate only if an iv route is indicated and analgesia is inadequate with repetitive doses.

Although CI was often effective when other methods were not, adequate analgesia was not achieved in more than one-third of the infusions. This finding confirms an earlier prospective study (12), in which four of 15 patients prescribed CI failed to achieve analgesia despite escalating doses. Similar to repetitive dosing, infusion rates can rise without analgesia until side effects, usually intolerable sedation, supervene. The failure of an opioid drug to provide analgesia despite maximally tolerated doses is a poorly understood phenomenon. In our series, it was most commonly observed in patients whose pain occurred episodically, usually with movement (so-called incident pain); in those with dysesthetic pain resulting from injury to an afferent sensory pathway (deafferentation pain); and in those whose pain was a component of a more global suffering not amenable to treatment by opioids.

Failure of CI with one medication may be followed by effective analgesia with another administered similarly, an observation well-described with repetitive oral opioid administration. Incomplete cross-tolerance is the most likely pharmacologic basis for this clinical experience. In one patient, a failed infusion with oxymorphone was successfully replaced with levorphanol, while in another, hydromorphone was useful where morphine was not. Unfortunately, sometimes no opioid works, as demonstrated by a 12-year-old girl with metastatic sarcoma who had significant pain until death despite CI with first methadone, then morphine, and finally hydromorphone.

Side effects during CI were common and included sedation, confusion, nausea, and vomiting. The retrospective nature of this review and the multiple drug therapies patients received preclude firm conclusions about the specific contribution of CI to these reactions. However, progressive adverse effects appeared to relate more to the medical deterioration of the patient than to CI itself. Transient, usually mild, respiratory effects have been described during morphone CI (12); these were clinically significant in only one of 15 patients evaluated in this study. The progressive somnolence reported (13) to complicate high-dose morphine CI as a toxic effect of the drug's preservative, chlorobutanol, could not be assessed directly, but is probably uncommon in routine CI. In the setting of progressive sedation, the risk of this toxicity can be obviated by the use of preservative-free solutions supplied by the hospital pharmacy.

Full assessment of toxicity was further complicated by the frequent prescription of CI to patients with terminal illness. Twenty-five of 46 infusions terminated with the death of the patient. In ten of these 25, the infusion was not decremented from the maximal rate, and most of the others were tapered minimally as patients became moribund. CI was continued in these patients despite the possibility that it may contribute to the clinical deterioration of these patients and precipitate death. The rationale for this practice lies in the belief that pain relief is the pre-eminent aspect of the supportive care offered the dying patient (14). The ethical issue raised by the continuation of a therapy with such potential toxicity as death approaches, and particularly as coma occurs, is one of many under discussion by those who treat these patients (14,15).

Guidelines for Use

The choice of drug for CI is dictated primarily by the patient's prior and current opioid experience. If adequate analgesia with side effects due to bolus effect is occurring, CI with the same medication is indicated. Large doses with minimal analgesia and excessive side effects warrant a change to an alternate opioid.

Pharmacokinetic factors are important in choosing the appropriate infusion drug. Steady-state plasma drug levels are not approached for four to five half-lives after CI begins (16). Although the rate at which the drug level rises and its ultimate steady-state concentration depend on the rate of infusion, the time to this steady state is dictated only by its half-life. For example, a methadone CI begun at a constant maintenance dose will not approach steady state for 4–5 days, since its half-life is approximately 15–24 hours (17). Thus, an increase in the maintenance rate in a patient with persistent pain risks both inadequate early analgesia as levels slowly rise and delayed toxicity as levels continue to rise for days after analgesia is attained. These difficulties can be ameliorated by the use of opioids with short half-lives, such as morphine (3–4 hours) or hydromorphone (2–3 hours) (18,19). The delay to steady state can be obviated altogether by the use of a loading bolus at the start of each increment in infusion rate. This is recommended for all infusion drugs. Unfortunately, the pharmacokinetic data are too meager to accurately predict the size of the loading dose, so that the risk of overshooting and causing transient toxicity remains.

Patients vary widely in their need for dose escalation during CI (fig 1). This poorly understood phenomenon relates to individual differences in the development of several interacting factors. These include the occurrence of tolerance, a pharmacologic property which de-

velops at varying rates to different opiate effects and is presumably due to changes at a receptor level, progression of underlying disease, and deterioration in the patient's psychological state with increasing pain complaints and suffering (20-22). As demonstrated in the review, opioid doses can become very high without compromising the functional status of the patient (12). In all patients, therefore, doses should be escalated until either analgesia or limiting side effects occur.

Accurate dosing during CI is a function of the infusion device. Recent experience has indicated that drop-rate-calibrated devices do not provide accuracy in CI (23), since flow rates can vary with different iv sets and solution viscosities. These fluctuations may pose an unacceptable risk to the patient receiving an opioid CI. The use of a flow-calibrated infusion pump will provide greater accuracy at less risk and should be required when CI of opioids is used.

Once the infusion drug is chosen, the following dosing guidelines of CI are suggested.

Conversion of opioid dosage to im equivalents.—The current total daily opioid consumption can be converted to im equivalents (table 1). For example, a patient who has consumed levorphanol (4 mg orally every 4 hours or 24 mg orally every 24 hours) has taken an amount equivalent to approximately 12 mg of levorphanol im every 24 hours. Although single-dose assays have found a 1:6 im-to-oral relative analgesic potency for morphine (11), this ratio probably changes in long-term dosing and a conversion of 1:2-3 is used clinically. Relative potencies between im and iv doses of the opioid analgesics have not been determined and are assumed to be equal for this calculation.

Use of current medication to begin infusion.—If the infusion is begun with the current drug, the maintenance rate will begin as this quantity added to solution and delivered over the next 24 hours. For example, if the maintenance infusion starts with the administration of 12 mg of levorphanol over the ensuing 24 hours, this quantity can be added to 500 ml of solution and delivered at a rate of 20 ml/hour.

Use of drug other than current medication to start infusion.—If an infusion drug other than the current medication is chosen, the quantity of the current drug administered per 24 hours and expressed as im equivalents must be converted to the im equivalent quantity of the infusion drug. Thus, 12 mg of levorphanol im/24 hours is equivalent to 60 mg of morphine im. Since cross-tolerance between different opioid drugs is incomplete, it is prudent to begin the maintenance rate with a total quantity equal to one-half this amount. In this example, the maintenance rate will be computed to deliver 30 mg of morphine to the patient during the ensuing 24 hours, eg, 30 mg added to 500 ml of solution administered at 20 ml/hour. A knowledge of pharmacokinetic differences is particularly important in switching from one opioid to another. If a short-half-life medication is replaced with an infusion drug of long half-life, accumulation of the drug can be expected to occur during the first few days of CI. Observation for adverse effects, particularly sedation, should be particularly close during this period. Infusion rates may need to be reduced after initial increases have their full effect. The clinician should also be aware that replacement of a longer-half-life drug with one of short half-life usually necessitates rapid increases in infusion rates during the first few days of CI, since body stores of the former drug are gradually eliminated.

Starting infusion with loading dose.—A loading bolus should be given at the start of the infusion. As noted, this must be chosen empirically, since there are inadequate pharmacokinetic data available to accurately predict the response at any dose. The following is a practical method with a low risk of toxicity: give a bolus of infusion drug equivalent to 15 mg of morphine if the maintenance rate is the morphine equivalent of ≤ 15 mg/hour; a bolus equaling the infusion rate if the maintenance rate is the morphine equivalent of 15-30 mg/hour (eg, a bolus of 20 mg of morphine if the infusion rate is 20 mg/hour); and a bolus equivalent of 30 mg of morphine if the maintenance infusion rate is equivalent to > 30 mg/hour of morphine. Bolus doses should be given as slow iv injections.

Monitoring vital signs.—After every bolus injection and change in maintenance infusion rate, vital signs should be taken every half hour for 4 hours. Patients do not need to be in special units to manage CI safely.

Varying infusion rate to increase analgesia.—There are two methods for increasing the infusion rate in the event of inadequate analgesia. The method chosen depends on the availability of close monitoring by a person capable of evaluating analgesic efficacy and side effects. If such monitoring is available, the patient should be assessed for several hours after the bolus injection is given and maintenance rate begun. Inadequate analgesia without intolerable side effects warrants a change in the CI at this time. The bolus injection should be repeated and the hourly infusion rate increased by 10%-20%. For example, a patient receiving an unsuccessful morphine infusion at approximately 30 mg/hour (eg, 720 mg of morphine added to a 500-ml solution and infused at 20 ml/hour) should receive a bolus injection of 30 mg and have the maintenance rate increased to 37 mg/hour (eg, 5 ml/hour). This procedure should be repeated every several hours until analgesia occurs or side effects result, specifically excessive sedation. An alternative method of incrementing the infusion rate is useful if resources are too limited to provide the close monitoring required by the above procedure. In this situation, a rescue dose of an opioid can be given on an as-needed basis. To reduce the risk of toxicity due to drug accumulation, this medication should be one with a short half-life. If the infusion drug has a short half-life, it should also be used as the

rescue medication; if not (eg, methadone CI), morphine is a reasonable choice. The dose of the rescue medication can be the equivalent to the loading bolus given every 3 hours as needed. A careful assessment of analgesia and side effects can then be made after 12-24 hours. Should the patient still have inadequate analgesia or if analgesia has been maintained only with the use of repeated rescue doses, the bolus injection should be repeated and the maintenance infusion rate increased as above. This process should also be repeated until adequate analgesia or intolerable side effects occur.

Trying alternatives for pain control.—The appearance of intolerable side effects which cannot be controlled with adjuvant drugs (eg, antiemetics for nausea) necessitates a trial of an alternative method of pain control. CI with a different opioid should be considered.

These guidelines, derived from the limited clinical and pharmacokinetic data now available, provide a rational basis for the use of opioid CI. Controlled studies will hopefully refine this outline and enhance the clinician's ability to optimize analgesia and minimize side effects with this technique.

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Randomized Dose-Response Evaluation of Etoposide in Small Cell Carcinoma of the Lung: A Southeastern Cancer Study Group Trial[1,2]

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To evaluate postulated dose-response relationships of etoposide (VP-16) for patients with recurrent small cell carcinoma of the lung, a prospectively randomized study was undertaken. VP-16 was administered iv at three dose levels: 300, 600, and 900 mg/m^2. Based on historical information, a 20% response rate was anticipated in the standard-dose level and the study was designed to be able to detect a response rate of 40% in either of the high-dose levels. The planned number of patients required in each arm was 45, with an α-level of 0.1 and a β-level of 0.2. The total number of patients actually entered was less than the planned number due to a low response rate. Seventy-seven of 79 treated patients were eligible, and 26, 27, and 26 patients were treated at each dose level, respectively. Toxicity was predominantly hematologic, with the higher dose levels substantially more toxic. Response to therapy was infrequent, with only four partial responses achieved and distributed between all dose levels. In this study, using previously treated patients, VP-16 at standard-dose or at moderate-dose increments had minimal activity. [Cancer Treat Rep 70:583–587, 1986]

Although considerable progress has been achieved in the treatment of small cell carcinoma of the lung (SCCL), long-term survival occurs only in a small minority of patients (1). Presently, combination chemotherapy is the mainstay of treatment (2). One of the critical aspects of effective combination chemotherapy is the use of each agent in optimal dose and schedule to achieve synergistic tumor cytotoxicity with subadditive overall toxicity (3).

Fostered by the success of intense chemotherapy and radiotherapy with bone marrow transplantation in the treatment of acute leukemia, drug dose-response relationships are being evaluated in various solid tumors (4). It is postulated that increased tumor cytotoxicity can be observed as doses of individual agents are escalated. Although increased overall toxicity is expected to occur with increased doses of chemotherapy, advances in patient-support techniques can sustain patients through such consequences as severe myelosuppression.

Etoposide (VP-16) is one of the active agents for the treatment of SCCL (5). Using transplantation of cryopreserved autologous bone marrow, VP-16 has been dose-escalated in a variety of neoplasms (6,7). From these studies, there are suggestions of improved efficacy with suprastandard dose but conclusive proof has been lacking.

In an attempt to study the dose-response relationship of VP-16 and to perhaps identify a more effective dose with tolerable toxicity, a prospective randomized multiinstitutional study was designed. VP-16 in three dose levels was randomly allocated to patients with recurrent SCCL. The first dose level was standard, the second was at the upper limits of standard therapy, and the third was three times the standard dose. From previous experience the higher dose levels were anticipated to be substantially myelotoxic, the dose-limiting side effect of VP-16 (8). This report shows the experience with these three dose levels of VP-16 in previously treated patients with SCCL and discusses the failure of the study to support the initial hypothesis.

MATERIALS AND METHODS

Patients were eligible for the study provided they had biopsy-proven SCCL, had undergone prior chemotherapy not including VP-16, and had recurrent and measurable disease. To be candidates for the higher dose levels, pa-

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tients had to be ≤ 65 years of age, had to have a life expectancy > 2 months and a Karnofsky performance status > 60% (able to care for themselves), and had to have normal peripheral blood cell counts (granulocyte count > 1500/μl and platelet count > 100,000/μl) without evidence of serious organ dysfunction not attributable to tumor. Informed consent approved by the individual institution was obtained prior to beginning treatment.

VP-16 was supplied by the National Cancer Institute (Bethesda, MD) and diluted in normal saline (1 ml/mg of drug). The maximum dose to be infused in 1 hour was 500 mg. For doses > 500 mg/day, consecutive equal infusions of half the daily dose were given.

Patients were stratified by extent of disease (limited vs extensive) and were randomized to one of three dose levels within each stratum: *Arm A*—100 mg/m^2 on Days 1-3 (total dose, 300 mg/m^2); *Arm B*—200 mg/m^2 on Days 1-3 (total dose, 600 mg/m^2); and *Arm C*—300 mg/m^2 on Days 1-3 (total dose, 900 mg/m^2).

Random numbers were generated using the SAS function uniform (9) and within each stratum were blocked in groups of six. Survival curves were plotted using the technique of Kaplan and Meier (10) and were compared using both the Gehan-Wilcoxon test (11) and the log-rank test (12).

After recovery of adequate blood cell counts (granulocyte count > 1500/μl and platelet count > 100,000/μl), a second course of chemotherapy was to be administered without dose adjustment.

Evaluation for therapeutic effect was performed after completion of two cycles of induction chemotherapy. Patients with disease progression were removed from the study. For responding or stable patients, therapy was to be continued at the initial dose level or, if toxicity was judged too severe, at the next lower dose level. Response and toxicity were evaluated by standard criteria of the Southeastern Cancer Study Group.

The projected sample size for each arm of the study was 46 patients, assuming an underlying binomial distribution and a significance test on the proportion, with an α-level of 0.1 and a β-level of 0.2 based on a response rate of 20% in Arm A and a detectable response rate of 40% in either Arm B or C. The primary endpoints of this study were response, toxicity, and survival. All data were submitted to the statistical center and each case was reviewed by the study chairmen.

Since this study was in part a toxicity study, interval evaluation prior to accrual of the total projected number of patients was undertaken. Early stoppage of the study was undertaken when the response rate of the high-dose arms was not significantly different from the standard-dose arm and the high-dose arms were associated with increased toxicity.

RESULTS

Seventy-nine patients were randomized for treatment; two were found to be ineligible. Thus, 77 patients comprised the study group whose characteristics are shown in table 1. Toxicity of induction chemotherapy was predominantly gastrointestinal (nausea, vomiting, or stomatitis) or hematologic. The percentages of patients exhibiting grade 3 (severe) or grade 4 (maximal or life-threatening) toxicity are shown in table 2. Six toxic deaths due to severe myelosuppression, sepsis, and hemorrhage occurred, one in Arm A, two in Arm B, and three in Arm C. The median absolute neutrophil count nadirs for Arms A, B, and C were 1500-1800, 300-600, and < 100/μl, respectively. The median absolute platelet count nadirs for Arms A, B, and C were > 120,000, 90,000-120,000, and < 30,000/μl, respectively. Due to tumor progression or severe toxicity, 11 patients on Arm A, nine on Arm B, and 11 on Arm C received only one course of chemotherapy.

Response to induction therapy was observed infrequently. One patient on Arm A had partial tumor response (one response among 26 patients), two on Arm B had partial response (two responses among 27 patients), and one on Arm C had partial response to therapy (one response among 26 patients). Overall survival for all patients from date on study is shown in figure 1. Twenty of 26 patients on Arm A have died from disease or toxicity compared to 23 of 27 on Arm B and 20 of 26 on Arm C. Median survival times for Arms A, B, and C were 12.6, 20.0, and 22.5 weeks, respectively. The difference in survival between any of the arms is not significant by either the log-rank or Gehan-Wilcoxon test.

DISCUSSION

In this study, VP-16 at three dose levels was administered to patients with previously treated SCCL. These dose levels ranged from standard to three times standard dose levels. We had hoped to confirm that VP-16 was active in previously treated patients and in addition demonstrate a greater response rate in the higher dose range supporting previously suggested dose-response relationships. Although substantial myelotoxicity at the higher doses was anticipated, previous studies at even higher doses were not associated with undue mortality in ambulatory patients. Unfortunately, no meaningful responses were noted in any of the treated patients, with only four partial responses among 77 patients (5%) documented. Although tumor cytotoxicity was not augmented, myelotoxicity was substantially increased as measured by neutrophil and platelet count nadir and by infectious complications. Due to minimal antitumor activity with substantial toxicity, the study was closed prior to the initial projected patient accrual.

The reasons for the therapeutic failure of this approach probably relate to the fact that pleiotropic drug resistance in previously treated patients with SCCL is difficult to overcome with single-agent therapy and that modest dose increments do not substantially alter that

TABLE 1.—Patient characteristics*

	Arm		
	A	B	C
	300 mg/m² (*N* = 26)	600 mg/m² (*N* = 27)	900 mg/m² (*N* = 26)
Performance status (Karnofsky)			
60%	—	4	—
70%	12	9	12
80%	7	11	8
90%	5	2	3
100%	2	1	3
Sex			
Male	15	25	21
Female	11	2	5
Prior chemotherapy			
1 prior regimen	23	21	19
2 prior regimens	3	5	3
3 prior regimens	0	1	4
Prior radiation therapy			
Yes	14	14	19
No	12	13	7
Prior surgery			
Yes	6	6	10
No	20	21	16
Age (yrs)			
< 50	5	3	4
50–60	10	15	12
> 60	11	9	8
Unknown	—	—	2
Extent of disease (not mutually exclusive)			
Opposite lung	5	4	1
Pleura	2	1	1
Liver	5	7	5
Brain	4	3	5
Bone marrow	4	4	3
Bone	4	8	6
Subcutaneous	1	2	1
Mediastinal lymph nodes	8	6	6
Supraclavicular lymph nodes	7	8	—

* Values = No. of patients.

TABLE 2.—% of patients with toxicity

	Arm		
	A	B	C
	(300 mg/m²)	(600 mg/m²)	(900 mg/m²)
Absolute neutrophil count nadir			
500–1000/μl	5	25	0
< 500/μl	0	54	86
Absolute platelet count nadir			
25,000–50,000/μl	0	0	24
< 25,000/μl	15	13	33
Nausea or vomiting, diarrhea, or stomatitis*			
Grade 3	5	4	10
Grade 4	0	0	0

* Grade 3 is intractable nausea or vomiting, bloody diarrhea, or stomatitis, making eating impossible; grade 4 is grade 3 toxicity requiring hospitalization.

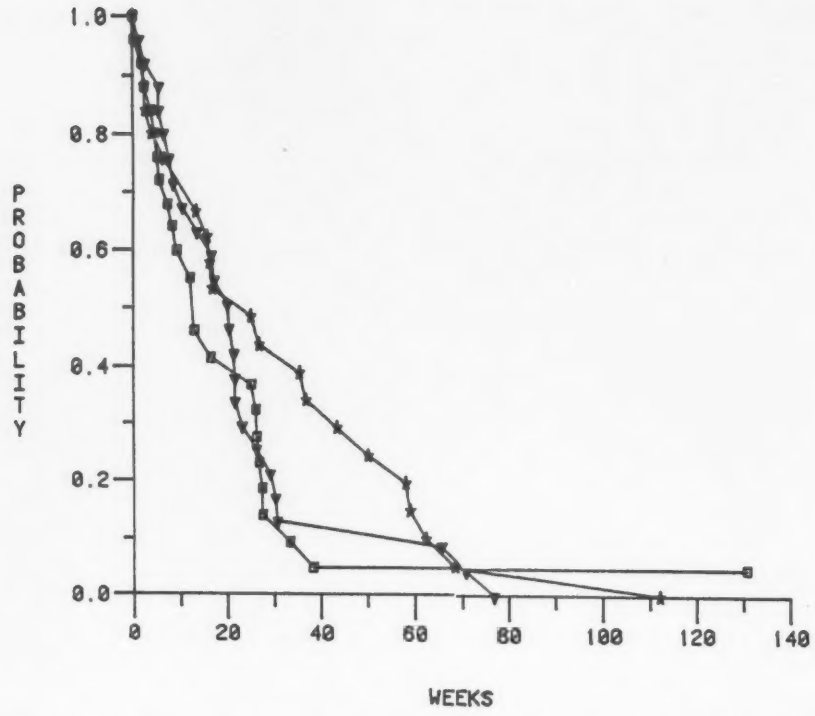

FIGURE 1.—Survival from date on study of all eligible patients. □ = Arm A (VP-16 at 300 mg/m^2); ▼ = Arm B (VP-16 at 600 mg/m^2); and ★ = Arm C (VP-16 at 900 mg/m^2).

situation. Supporting this concept is the observation of markedly enhanced activity of single-agent therapy in refractory tumor only at marked dose increments over standard dose increments (7,13). Recently, other studies have failed to demonstrate meaningful tumor activity of VP-16 against SCCL at standard dose or at slight dose escalations (14). VP-16 thus appears to be relatively inactive in patients who have previously received cyclophosphamide, doxorubicin, and vincristine, and within the dose ranges given in our study, this was also true.

Although a slight prolongation of median survival of patients treated on the highest-dose arm was noted, no meaningful benefit was derived from any of the treatment arms. In summary, VP-16 at standard dose or at modest dose increments has minimal activity against previously treated patients with SCCL.

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Frequency and Diversity of Use of Statistical Techniques in Oncology Journals[1,2]

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We describe the frequency with which various statistical techniques are reported in almost 5000 articles published in five major American oncology journals during 1983 and 1984. A reader familiar with about a dozen techniques can expect to understand approximately 90% of the quantitative concepts cited in these journals. With the exception of survival analysis, these were typically the techniques encountered in many introductory statistical texts. Oncology training program preceptors concerned about making their graduates more effective consumers of the literature can use these findings in structuring exposure to quantitative skills. In four of the five journals reviewed, failure to identify the statistical methodology was among the ten most commonly encountered "techniques." This made it impossible to identify the analytical procedures used in many articles, and hence to judge their scientific validity. We encourage more editorial boards to adopt guidelines requiring a standardized format for presenting results based on a statistical analysis. [Cancer Treat Rep 70:589–594, 1986]

All physicians and biomedical researchers face the challenge of keeping abreast of a body of biological knowledge that is expanding at an astonishing rate. The current views on the causes, mechanisms, and treatment of disease are advancing too rapidly for any physician or scientist to have personal experience with each new finding. In general, this has led to a growing reliance on the published literature to learn about new biomedical discoveries that can ultimately influence therapeutic decisions.

One of the most important functions of any medical journal is the effective dissemination of scientifically valid research findings (1–11). To evaluate an article's scientific merit, a reader should be familiar with the methodology described, especially the kinds of issues that can arise when quantitative techniques, such as statistical procedures, are used to champion hypotheses, improve the understanding of a research finding, or summarize a large volume of raw data.

The purpose of this report was to ascertain the actual frequency with which various statistical concepts were mentioned in the major American oncology journals. We wished to answer questions such as: How often are various statistical techniques reported in these journals? Which statistical methods are mentioned most often in oncology journals compared to more general journals such as the *New England Journal of Medicine* (*NEJM*) (3)? Do readers of clinical versus basic science oncology journals need different statistical expertise?

With limited time and teaching resources available, questions arise about what quantitative issues to teach oncologists (in-training) or where in the curriculum to locate such exposure (12,13). Improving the statistical literacy of oncologists by identifying those techniques needed to read the literature may help those responsible for oncology training programs ensure that their graduates acquire the skills they need to be effective consumers of the oncology literature (7,14).

MATERIALS AND METHODS

This study inventoried the statistical techniques reported in 4983 articles appearing in the 1983 and 1984 issues of five oncology-oriented journals [*Cancer Treatment Reports* (volumes 67 and 68), *Cancer* (volumes 51, 52, 53, and 54), *Cancer Research* (volumes 43 and 44), *JNCI* (volumes 70, 71, 72, and 73), and *Journal of Clinical Oncology* (volumes 1 and 2)]. Editorials, case reports, and review articles were evaluated, although the majority did not mention statistical methodology. Letters,

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meeting notices, and other short commentaries were excluded from analysis. While other journals could have been included, this sample represents the major American medical oncology journals and covers the spectrum of clinical and basic science oncology literature. Surgical oncology, radiation oncology, and other oncology subspecialty journals were not reviewed.

To standardize the enumeration of statistical usage in these journals and allow comparison with other medical literature, the categories used to assess statistical content (table 1) were based on an article by Emerson and Colditz (3). Each statistical procedure was counted only once per article, regardless of the number of times mentioned in that article. For example, if an author said multiple comparison tests (MCT) following analysis of variance (ANOVA) were not performed, then both MCT and ANOVA were scored. We recorded whether a particular statistical concept was reported, not whether it was used correctly.

TABLE 1.—Categories used to assess statistical content of oncology journals

Category	Brief description
1. Descriptive statistics	Means, medians, and modes
2. Contingency tables	Chi-square tests, Fisher's exact test, McNemar's test, Yates' correction
3. Multiway tables	Mantel-Haenszel procedure, log-linear models
4. Epidemiologic statistics	Relative risk, odds ratio, log odds, measures of association, sensitivity, specificity
5. t-tests	1-sample, matched-pair, and 2-sample t-tests
6. Pearson correlation	Bivariate product-moment correlation
7. Simple linear regression	Least-squares regression with 1 predictor and 1 response variable
8. Multiple regression	Includes polynomial regression and stepwise regression
9. Analysis of variance	Analysis of variance, analysis of covariance, and F-tests
10. Multiple comparisons	Multiple inferences on same data sets (eg, Bonferroni techniques, Scheffe's contrasts, Duncan multiple-range procedures, Newmann-Keuls procedure)
11. Nonparametric tests	Sign test, Wilcoxon signed-rank test, Mann-Whitney test, etc.
12. Nonparametric correlation	Spearman's rho, Kendall's tau, test for trend
13. Life table	Actuarial life table, Kaplan-Meier or Berkson-Gage estimates of survival
14. Regression for survival	Includes Cox proportional hazard and logistic regression
15. Other survival analysis	Breslow's Kruskal-Wallis, Lee-Desu, Gehan's, log ranks or Cox's model for survival comparison
16. Power	Not well defined, includes use of the size of detectable (or useful) difference in determining sample size
17. Transformation	Use of data transformation (eg, logs)
18. Dispersion	Standard deviations, standard errors of the mean, ranges, etc
19. Unspecified test	Use of a statistical test of significance without explicit identification of methodology
20. Other	Anything not fitting above headings; includes cluster analysis, discriminant analysis, mathematical models, Scatchard plots, Lineweaver-Burk plots and pharmacokinetic models, cost-benefit analysis

We considered one category (no statistics or descriptive statistics only) in the Emerson and Colditz (3) report to be too comprehensive and subdivided it into three different categories. Our tables differentiate between articles that did not explicitly mention any statistical methodology or just counts and percentages (typically case reports, morphological reports, photomicrographic essays, etc), those that calculated a statistic describing a central tendency (mean, median, mode, etc) (Category 1 in table 1) either by itself or as part of a more complex analysis, and those that reported the concept of dispersion (standard error of the mean, standard deviation, range, etc) (Category 18).

Articles that did not mention explicitly the methods used, but reported the statistical significance of a hypothesis test [ie, a "*P* value not otherwise specified" (NOS)] that could not be linked to a particular statistical method were also tabulated separately (Category 19). In a given article, if a "*P* value" was reported, we attempted to determine if it could be ascribed to an explicitly described statistical technique or bibliographical reference.

Three categories from the *NEJM* (3) article occurred very infrequently in the oncology literature reviewed. For both years in the five journals studied, there were less than eight occurrences of the "adjustment and standardization," "sensitivity analysis," and "cost-benefit" categories as listed in the Emerson and Colditz article (3). For this report, they were combined into the "other" category.

One individual (J. A. Hokanson) read and tallied the statistical content of all articles reviewed in our study. While this implies that our results depend on the qualifications and biases of this individual, we chose to ensure that all 4983 articles were judged according to similar criteria. This method offered the best quality control alternative available, since if biases were imparted by the reader, they should have applied to all journals equally. It also eliminated inter-reviewer variability and the need for a formal training program to ensure that all reviewers used the same assessment criteria. This process of counting reported techniques was different from a situation where a reader must judgmentally classify a report into arbitrary categories or evaluate the "quality" of the research. The major type of error expected would be an under-reporting of statistical usage. While it is possible that the reader may have occasionally missed the listing of a procedure, it is highly unlikely that he added, systematically, techniques not actually reported.

To assess the reliability of our empirical survey, a 5% sample (250 articles) was selected for a second reading using a computer-based randomization technique. Two discrepancies in the frequencies of statistical concepts inventoried were noted in the 250 articles surveyed twice. While not perfect concordance, it is an error rate that

should not lead to major inaccuracies in inferences from our study.

Since it was never the intention of this study to compare analytically the relative sophistication of oncology journals, only reported frequencies of statistical use were tabulated. For each article, the occurrence of each statistical method category (table 1) was noted. From this, the overall frequency distribution of statistical techniques reported for the entire volume of a journal was then determined (15).

RESULTS

Table 2 shows the relative distribution with which each statistical method was used in the oncology journals reviewed. An obvious finding is the frequent use (55%–94%) of statistical methodology in every journal. Even when references to descriptive statistics (Categories 1, 2, and 19 in table 1) are eliminated, there is still a large fraction of articles requiring statistical expertise in order to appreciate the methodology reported. With the exception of survival analysis and pharmacokinetic modeling (which we listed under "other" to conform to the *NEJM* categories), the majority of topics across all oncology journals reviewed were similar to those reported for the *NEJM* (3) and typically covered in many introductory statistics texts.

There are clear demarcations in the patterns of statistical usage among the various oncology subspecialty journals. The *Journal of Clinical Oncology* used life tables in 44% of articles in 1983, while this technique was used in only 1.6% of the articles in *Cancer Research*; multiple comparisons were common in *JNCI* and rare in the *Journal of Clinical Oncology*.

Category 20 ("other") observations often represented results reported as mathematical functions. These were not simple linear transformations but often complex mathematical relations between independent and dependent variables. The majority of the methods listed as "other" were represented by four techniques (Lineweaver-Burk plots, Scatchard analyses, reciprocal dose-response curves, or other pharmacokinetic models). Because they were not a separate category of statistical techniques reported in the *NEJM* articles, pharmacokinetic models or reciprocal dose-response curves were not explicitly counted in our survey. However, readers of *Cancer Research* or *Cancer Treatment Reports* will need to be familiar with these techniques since they are very commonly used in these journals.

For each journal, there was a great similarity in statistical methodology for the 2 years studied. For ease of interpretation, table 3 combines the 2 years and shows the ten most frequently used statistical procedures in order of decreasing frequency of use for each reviewed journal.

TABLE 2.—Distribution of statistical techniques in 5 oncology journals (1983–84)*

	JNCI		*Journal of Clinical Oncology*		*Cancer Treatment Reports*		*Cancer Research*		*Cancer*		*All journals*		
Statistical technique	1983	1984	1983	1984	1983	1984	1983	1984	1983	1984	1983	1984	1983–84
1. Descriptive statistics	42.7	62.1	52.7	20.3	43.8	41.1	57.0	64.8	41.8	33.4	48.6	46.7	47.6
2. Contingency tables	15.1	16.5	15.7	20.3	4.5	4.9	7.3	6.1	13.2	10.5	10.4	10.4	10.4
3. Multiway tables	4.7	6.0	1.8	.4	1.3	.0	.6	.3	2.5	2.0	1.9	1.7	1.8
4. Epidemiologic statistics	6.5	6.8	1.8	3.3	1.3	1.0	2.3	1.1	4.0	2.6	3.3	2.7	3.0
5. t-test	13.9	18.4	5.5	5.9	4.5	3.8	15.3	18.8	7.4	7.1	11.1	11.8	11.4
6. Pearson correlation	5.6	4.7	.9	2.9	2.2	1.0	5.5	2.9	3.7	2.7	4.4	2.9	3.6
7. Simple linear regression	5.9	6.8	.9	1.6	3.1	.0	6.0	4.9	2.3	1.5	4.3	3.1	3.7
8. Multiple regression	2.0	.2	1.8	2.5	1.8	.7	.9	1.5	1.1	1.0	1.2	1.1	1.2
9. Analysis of variance	6.2	5.2	2.7	2.1	3.6	.7	1.5	1.9	.3	.4	2.0	1.8	1.9
10. Multiple comparisons	3.2	4.7	.0	.8	.4	.7	1.5	1.9	.3	.4	1.2	1.6	1.4
11. Nonparametric tests	5.6	4.2	4.6	4.6	2.2	2.8	3.9	5.1	3.9	4.3	4.0	4.4	4.2
12. Nonparametric correlation	.2	1.3	.9	.8	.0	.7	.8	.7	1.3	.5	.8	.7	.8
13. Life tables	2.6	5.0	44.4	30.5	8.1	13.0	1.6	2.9	21.3	18.0	10.7	12.2	11.5
14. Survival from regression	2.0	3.9	8.3	8.4	1.8	.3	2.2	1.0	3.3	2.8	2.8	2.7	2.7
15. Other survival analysis	2.0	1.0	1.0	19.9	4.9	5.9	2.1	2.2	12.5	10.8	5.7	7.1	6.4
16. Power	.5	7.7	1.8	4.6	.4	.3	.0	.1	.1	.0	.2	1.6	.9
17. Transformations	2.9	4.2	3.7	.4	5.4	1.7	12.5	2.9	2.0	1.9	6.7	2.4	4.5
18. Dispersion	41.3	56.8	18.5	8.8	32.5	18.3	53.6	61.2	22.7	21.2	38.2	37.0	37.6
19. Unspecified test	3.5	7.3	5.5	3.8	6.3	4.5	7.8	5.9	4.6	4.9	5.9	5.4	5.7
20. Other	7.4	10.7	11.1	6.7	18.9	5.9	42.7	25.9	5.2	10.3	21.9	14.2	18.0
Total No. of articles	337	380	108	236	221	284	972	754	810	881	2448	2535	4983
No. of articles containing no statistical methods	49	23	14	46	79	102	155	163	344	394	641	728	1369
% of articles containing statistical methods	85.5	94.0	87.0	81.5	64.3	64.1	84.1	78.4	57.6	55.3	72.9	71.3	72.6

* Unless otherwise specified, values = % of articles containing this method.

Also listed is the percentage of cited techniques accounted for by these ten methods.

The two most commonly used statistical techniques for four of the five journals were statistics describing a central tendency and measures of dispersion. If these techniques had been excluded, life table methodology was the most frequently used statistical technique in the oncology literature. The next most commonly used technique was the t-test.

There is a great deal of overlap in the methodology used in both the oncology and general medical literature, yet it is clear that readers of oncology journals must be familiar with survival analysis and pharmacokinetic models (listed as "other" in our tables) in addition to the techniques used in the more general literature. Unfortunately, a failure to identify the techniques used (*P* value NOS) was among the top ten most frequently encountered situations in four of the five oncology journals reviewed.

Table 4 provides a composite ranking from the literature we reviewed compared to that found in the *NEJM* article. For the purpose of this table we did not include our category "dispersion," so we used our category of "means" to describe descriptive statistics. Table 4 suggests that even though the frequency of use varies from journal to journal, a reader familiar with about a dozen statistical procedures [descriptive statistics, contingency tables, epidemiologic statistics, t-test, simple linear regression, analysis of variance, life tables, regression for survival, survival comparisons, transformation, dispersion, and other (primarily pharmacologic modeling)] will be familiar with approximately 90% of the techniques reported in all of the oncology journals surveyed.

DISCUSSION

Today, because of an increasing dependence on the literature, publication of a clinical investigation or laboratory finding promptly affects both the practice of medicine and its research directions. The strength of the conclusions reported in many articles is often based on statistical methodology. We have identified the frequency with which statistical concepts were mentioned in recent volumes of five American oncology journals. Our findings suggest that to understand the methodology reported in many of these journals, oncologists need statistical skills beyond those of readers of more general medical journals (2-4). Familiarity with survival curve analysis and pharmacokinetic modeling is important to the reader of the oncology literature. Wallenstein et al (10) suggest that ANOVA techniques are important to readers of *Circulation*; ANOVA was among the top ten techniques in only two of the journals we reviewed.

We also report anecdotally, as we have previously noted for other literature, that measures of dispersion were often described ambiguously (16) in the oncology journals. The standard error of the mean was frequently used to describe the dispersion within a single sample (the standard deviation could then be calculated if the sample size was also reported).

Many studies rejecting a null hypothesis of no difference between treatment reports did not discuss the probability of being able to detect a difference if it existed (the concept of statistical power), or when the strength of effect is too small for the sample size chosen. The fact that relatively few articles mentioned the concept of statistical power confirms that many researchers place insufficient emphasis on this important concept (17). Some articles reported that all differences were "not statistically significant," without indicating that statistical power had been considered. A larger fraction of articles indicating that the statistical power had been calculated would have been reassuring.

One "error" described in this report was the omission of a statement specifying the actual methods used when a "*P* value" resulting from a statistical test of a hypothesis was included (listed in tables as "unspecified test"). Technically, this could be viewed as more of a reporting oversight than a misuse of statistical methodology. Unfortunately, this omission was one of the ten most common-

TABLE 3.—Ten most commonly mentioned statistical techniques in the 1983-84 editions of 5 American oncology journals*

JNCI (87.1)	*Journal of Clinical Oncology* (88.8)	*Cancer Treatment Reports* (90.0)	*Cancer Research* (92.4)	*Cancer* (87.6)
1. Descriptive	1. Life tables	1. Descriptive	1. Descriptive	1. Descriptive
2. Dispersion	2. Descriptive	2. Dispersion	2. Dispersion	2. Dispersion
3. t-test	3. Other survival analysis	3. Life tables	3. Other	3. Life tables
4. Contingency tables	4. Contingency tables	4. Other	4. t-test	4. Contingency tables
5. Other	5. Dispersion	5. Other survival analysis	5. Transformations	5. Other survival analysis
6. Epidemiology statistics	6. Survival from regression	6. Unspecified test	6. Unspecified test	6. t-test
7. Simple regression	7. Other	7. Contingency tables	7. Contingency tables	7. Other
8. Analysis of variance	8. t-test	8. t-test	8. Simple regression	8. Unspecified test
9. Multiway tables	9. Nonparametric tests	9. Transformations	9. Analysis of variance	9. Nonparametric tests
10. Pearson correlation	10. Unspecified test	10. Nonparametric correlation	10. Nonparametric tests	10. Epidemiology statistics

*See table 1 for description of categories. Values in parentheses = the cumulative % of statistical techniques represented by the 10 most commonly mentioned procedures. For example, for *Cancer*, a reader understanding the 10 techniques listed would be familiar with > 87% of the statistical techniques mentioned in this journal.

TABLE 4.—The 10 most commonly mentioned statistical techniques in a general medical journal and the oncology literature*

New England Journal of Medicine† (87.4)	Oncology literature (89.2)‡
1. Descriptive	1. Descriptive statistics
2. t-test	2. Other
3. Contingency tables	3. Life tables
4. Nonparametric tests	4. t-test
5. Epidemiology statistics	5. Contingency tables
6. Pearson correlation	6. Other survival analysis
7. Simple regression	7. Unspecified test
8. Analysis of variance	8. Transformations
9. Transformations	9. Nonparametric tests
10. Nonparametric correlation	10. Simple linear regression

*Values in parentheses = the cumulative % of statistical techniques represented by the 10 most commonly mentioned procedures.

†*See* ref 3.

‡For comparison purposes, in this column descriptive statistics means the reporting of a mean, median, or mode.

ly reported categories for four of the five oncology journals. In these instances, the methodologic identification was sometimes described by phrases such as "analysis was done by computer," "the usual statistics were done," "impaired t-test," "lifetime table methods," or "paired analysis."

We suggest that this is an unsatisfactory practice and that an appropriate reporting standard should include statistical analyses described in sufficient detail so a reader could reproduce the calculations if the data were available. We suggest that every test of statistical significance should be accompanied by an unambiguous identification of the technique, the data source, and the rationale for the population sample chosen. While investigators often have valid reasons for weaknesses in design of studies, reasons for weaknesses in reporting can be few. As a standard part of their instructions for authors, we recommend that more editorial boards require a standardized format for the reporting of results that are based on a statistical analysis (18-23). Journals such as *Cancer Treatment Reports* (23) and the *American Journal of Psychiatry* have recently done so.

A full statistical understanding of an article requires more than a superficial knowledge of the methodology used. In addition to familiarity with particular tests, general issues in statistical inference should be appreciated (1,24). However, a listing of the commonly used techniques is a starting point for establishing criteria for the quantitative content of oncology training programs (3).

Our study was designed to describe the frequency with which statistical techniques are reported in the oncology literature and not to determine the "proper" use of statistical methodology within each article; evaluation of the "appropriate" statistical techniques for a particular article is a complex process, involving authors, reviewers, and editorial staff. Guidelines for the use of particular statistical techniques may fail to apply in many circumstances or only marginally improve the ultimate clinical usefulness of numerous reports (19-22).

If computer software packages are employed for more than simple counts, percentages, or cross tabulations, the specific package and the procedures used should be identified or referenced. The intent should not be to dictate limits for statistical usage, but to ensure that if authors choose to employ a computer-based statistical analysis, the techniques used should be reported in an unambiguous format (8,20-23). The clarification of the use of statistical methodology has the potential to greatly enhance the scientific contribution of many articles in the oncology literature and thereby increase the ability of this literature to effectively serve in efforts to improve the diagnostic accuracy and resulting treatment of neoplastic disease (5).

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High-Dose Teniposide for Refractory Malignancies: A Phase I Study[1]

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To evaluate the dose-limiting toxicity of teniposide (VM-26), a phase I study was conducted. VM-26, a semisynthetic podophyllotoxin derivative, was administered on 3 consecutive days. The initial total dose per course was 0.3 g/m^2, with dose escalation to 0.6 and 1 g/m^2. The most prominent side effects observed were severe skin rash in all three patients in the highest dose group and a dose-dependent degree of leukocytopenia and thrombocytopenia. In the highest dose group the leukocyte count in all courses was $< 1 \times 10^9$ cells/L and in three of five courses the platelet count was $< 25 \times 10^9$ cells/L. Of the 13 evaluable patients, five had partial remission, one had minor response, and four had stable disease. Further study should be centered on phase II studies in selected tumor groups at a VM-26 dose of 0.6 g/m^2. [Cancer Treat Rep 70:595–598, 1986]

Teniposide (VM-26), a semisynthetic podophyllotoxin derivative, is active against a number of tumors at a standard dose of 70–180 mg/m^2 per 3 weeks (1). This dose was determined in phase I studies, accepting only a modest degree of myelosuppression (1–3).

Today, in clinical practice, much more severe hematologic toxicity is accepted, eg, in the treatment of acute leukemia and small cell lung cancer (SCLC). This is the result of improved supportive care, including infection prevention; platelet transfusion; and feeding (4,5). From various experimental in vivo studies, there is evidence that for most cytostatic drugs a positive dose-response relationship can occur at dose levels above the standard dose (6).

Etoposide (VP-16-213), another semisynthetic podophyllotoxin derivative, has been proven to be an ideal drug for dose augmentation. Doses of VP-16-213 up to 3.5 g/m^2 were given, which resulted in temporary myelosuppression. At a dose of 3.5 g/m^2, oropharyngeal mucositis (7) was found to be dose-limiting.

For the podophyllotoxin derivatives, a dose-dependent activity was found in both mouse and human tumor cell lines in vitro (8–10). The same relation is suggested in vivo in patients treated with VP-16-213 for germ cell cancer (11) or SCLC (12). Furthermore, the antitumor effect for VM-26 was enhanced with repeated as compared to single drug injections (13,14).

To evaluate the dose-limiting toxicity of VM-26 more extensively, we started a phase I study using a 3-day regimen.

MATERIALS AND METHODS

Patients

From April 1983 to February 1984, a total of 18 patients with disseminated malignancies were entered in a phase I study with high-dose VM-26. Eligibility criteria for the study were: age < 70 years, leukocyte count $\geq 3.0 \times 10^9$ cells/L, platelet count $\geq 100 \times 10^9$ cells/L, no signs of bone marrow involvement, Karnofsky score ≥ 50, normal renal function (serum creatinine ≤ 150 μmols/L), normal bilirubin (≤ 25 μmols/L), normal SGOT and SGPT, and the absence of available effective therapy. Biochemical abnormality at the start of therapy was elevated LDH in two patients. Informed consent was obtained from all patients. None of the patients were previously treated with VM-26, while two were treated with VP-16-213.

VM-26 Administration

VM-26 was administered on 3 consecutive days. The starting dose for this study was 0.3 g/m^2. The subsequent dose levels were 0.6 and 1.0 g/m^2. One-third of the total drug dose was diluted in 1 L of normal saline (maximum

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concentration, 0.8 mg/ml) and administered iv over a period of 2 hours. Dose escalations were to proceed if no unacceptable toxicity was seen in any of at least three patients at that level. Unacceptable toxicity, using the World Health Organization (WHO) grading system (15), was defined as grade 4 oral mucositis, grade 3 diarrhea, grade 4 dermatitis, grade 3 neurotoxicity, or grade 4 hematologic toxicity in > 50% of the patients. To be evaluable for toxicity the patient had to survive for at least 4 weeks from start of treatment.

All patients received VM-26 on an inpatient basis. Cbc and blood chemistries, including BUN, creatinine, electrolytes, bilirubin, γ-glutamyl transferase, alkaline phosphatase, SGOT, SGPT, and LDH, were obtained twice a week. Selective decontamination of the digestive tract (4) with oral antibiotics and oral amphotericin B was used as infection prevention if the leukocyte count was $< 1 \times 10^9$ cells/L. Platelet transfusions were given when bleeding was present or prophylactically if the thrombocyte count was $< 15 \times 10^9$ cells/L. Infection was defined as clinically or bacteriologically documented infection.

Treatment courses were repeated at the same dosage after 3 weeks if no disease progression was present and no unacceptable toxicity was seen.

Response

To be evaluable for response the patient had to be followed for at least 4 weeks after the start of treatment.

Lesions were considered measurable in the case of a lung tumor surrounded by aerated lung, a skin nodule, and a superficial lymph node. Lesions were considered evaluable in the case of a lung tumor not completely surrounded by aerated lung, a palpable deep lymph node, hepatomegaly with the inferior liver edge palpable at least 5 cm below the costal margin, and liver lesions with a diameter of at least 2 cm (demonstrated only by ultrasound or computer tomography).

Complete remission was defined as the disappearance of all signs and symptoms of detectable tumor. Partial remission was defined as a decrease in size of at least 50% of the sum of the products of the largest perpendicular diameters of measurable lesions. Stable disease was defined as no change or a decrease of < 50% of the sum of the products of the largest perpendicular diameters of measurable lesions. Disease progression was defined as a 25% increase of the lesions, measured in the same way. Subjective response was defined as improvement of pain due to tumor involvement.

RESULTS

Patients

Of the 18 patients entered in the study, seven were male and 11 were female, with a mean age of 53.3 years (range, 34-70). Nine patients received more than one course, seven of these more than two courses of VM-26.

Fifteen patients were heavily pretreated with combination chemotherapy with or without radiotherapy (table 1).

Nine patients received only one course due to the progressive nature of the disease.

Nonhematologic Toxicity

Moderate nausea and vomiting, easily controllable by antiemetic therapy, occurred in nine patients (50%). One patient had mild diarrhea (WHO grade 1), and four had mild mucositis (WHO grade 1). Complete hair loss occurred in all patients without alopecia due to prior therapy. One patient who received a second course with 1 g/m^2 of VM-26 and had no previous therapy except doxorubicin developed paresthesias and had an abnormal electromyography. This was completely reversible. None of the patients had hypotension during or after the infusion of VM-26, one had fever after the third dose, and one felt dizzy and was dyspneic during infusion of the drug. At the 1-g/m^2 dose one patient had mild elevation of SGOT and SGPT (WHO grade 1). Only the three patients in the highest dose group developed an intensively pruritic erythematous rash with purpura 4-7 days after the start of the chemotherapy. The rash involved the upper part of the chest and both upper legs. In two patients ulceration was seen (WHO grade 3). The rash cleared spontaneously within 1 week; no therapy with steroids or antihistamines was started. Two of these patients received a second course of VM-26 with a 50% dose reduction. In both patients no rash occurred during the second course with the reduced dose.

Hematologic Toxicity (table 2)

The degree of leukocytopenia and thrombocytopenia was dose-dependent. In the highest dose group the leukocyte count was $< 1 \times 10^9$ cells/L in all courses and the platelet count was $< 25 \times 10^9$ cells/L in three of five courses.

Infections occurred only at the time of the leukocyte count nadir. At the 0.6-g/m^2 dose level, only one patient with hypernephroma had a urinary tract infection with *Escherichia coli*. At the 1-g/m^2 dose level, there were infections during three of the five courses. One patient with liposarcoma had two clinical infections with fever > 38.5°C without focus and one patient with adenocarcinoma of unknown origin had *Escherichia coli* septicemia. All infections responded to antibiotic treatment. No treatment-related deaths occurred.

Response (table 1)

Of 13 evaluable patients, five achieved partial response, one had minor response, four had stable disease, and three had disease progression. All partial responses

TABLE 1.—Patient characteristics

Patient No.	Diagnosis	Previous therapy*	Karnofsky performance score	No. of courses	Response†
		0.3 g/m²			
1	Ovarian carcinoma	L-PAM	80	5	PR
2	Ovarian carcinoma	L-PAM, ADM, CDDP	90	1	NR
3	Ovarian carcinoma	CTX, HMM, CDDP	80	1	NR
4	Liposarcoma	CTX, VCR, ADM, DTIC	80	4	PR
5	Leiomyosarcoma	ADM	100	7	PR
6	Planocellular carcinoma, lung	—	50	1	NE
7	Small cell carcinoma, lung	VDS, CTX, ADM, VP-16-213	70	1	NR
		0.6 g/m²			
1	Small cell carcinoma, lung	CTX, CDDP, ADM, VP-16-213, PCZ, VCR	80	1	NR
2	Breast carcinoma	CTX, ADM, 5-FU	70	2	NE
3	Leiomyosarcoma, uterus	ADM	100	2	MR
4	Colon carcinoma	—	90	3	NR
5	Adenocarcinoma, uterus	CTX, ADM, CDDP	80	1	NR
6	Hypernephroma	—	70	4	PR
7	Melanoma	TNO6, Bleo, DTIC	70	2	NR
8	Adenocarcinoma, unknown origin	—	70	1	NE‡
		1.0 g/m²			
1	Adenocarcinoma, unknown origin	—	80	1	NE‡
2	Adenocarcinoma, lung	—	80	1	NE
3	Liposarcoma	—	100	3	PR

*L-PAM = melphalan; ADM = doxorubicin; CDDP = cisplatin; CTX = cyclophosphamide; HMM = hexamethylmelamine; VCR = vincristine; DTIC = dacarbazine; VDS = vindesine; PCZ = procarbazine; TNO6 = spiroplatin; and Bleo = bleomycin.

†PR = partial response; NR = no response; NE = not evaluable; and MR = minor response.

‡Improvement of pain due to bone metastases.

curred after the second course; one minor response occurred after one course. In two patients without evaluable tumor lesions, subjective improvement of pain due to bone metastases of adenocarcinoma of unknown origin was seen. Table 1 shows diagnoses and treatment results for the different patients. The number of patients is too small to find a relation between the dose of VM-26 and the response.

DISCUSSION

VM-26 has been proven to have a role in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, bladder carcinoma, neuroblastoma, and childhood acute lymphoblastic leukemia. There has been some activity noted against a spectrum of adult solid tumors including malignant gliomas and carcinomas of the breast, colon, and ovary (1,2,14,16–18). There are, however, two major problems with the studies which have produced the results. The first problem is that the number of patients used in many of the studies is quite small and may therefore be unreliable. The second problem is that most of the data are flawed by the absence of conclusive trials in these malignancies (19). From all the studies until the present one, the maximally tolerated dose of VM-26 has not been determined (19).

In this dose escalation study, we found that both 0.3 and 0.6 g/m² of VM-26, if divided over 3 consecutive days, could be safely administered to patients. This escalation resulted only in minor side effects.

TABLE 2.—Hematologic toxicity of VM-26

Dose (g/m^2)	No. of courses (No. of patients)	No. of courses (%), leukocyte count < 1 × 10^9 cells/L	Mean leukocyte count nadir, × 10^9 cells/L (range)	Day of leukocyte count nadir*	No. of courses (%), platelet count < 25 × 10^9 cells/L	Mean platelet count nadir, × 10^9 cells/L (range)	Day of platelet count nadir*	No. of infections (%)
0.3	20 (7)	4 (20)	2.03 (0.1-3.9)	10.8	1 (5)	132.7 (10-200)	11.3	0
0.6	16 (8)	7 (43.7)	1.39 (0.4-2.6)	10.6	3 (18)	101.1 (13-211)	11.6	1 (6.2)
1.0	5 (3)	5 (100)	0.29 (0.07-0.4)	12.7	3 (60)	37.0 (12-80)	11.0	3 (60)

* From start of chemotherapy.

Hematologic toxicity proved to be clearly dose-dependent. The dose-limiting toxicity of VM-26 at 1 g/m^2 is hematologic and dermatologic toxicity. All patients in this dose group had leukocyte counts < 1 × 10^9 cells/L and during three of five courses they did need platelet transfusions. All three patients receiving the maximal dose developed skin rash; two had grade 3 dermatitis. In two of these patients no rash appeared during a second course with a 50% dose reduction of VM-26; this makes an allergic reaction due to VM-26 as the cause of the rash in the first course less likely. One patient had reversible neurotoxicity (grade 2).

It is promising that 38% (five of 13) of the evaluable patients in this phase I study achieved partial response, one had minor response, and two had subjective response with improvement of bone pain due to tumor involvement. It is important to note that in all patients two courses were necessary to achieve partial response. Due to the phase I nature of the study, it is impossible to draw conclusions on the efficacy of higher doses as well as the relation between performance score, prior therapy, and the effect of VM-26.

Further study should center on the performance of phase II studies in selected tumor groups at a VM-26 dose of 0.6 g/m^2.

Further, pharmacokinetic studies must be performed to decide whether the administration scheme of VM-26 in this study was optimal.

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Phase I Study of Triglycidylurazol Given on a 5-Day Iv Schedule[1,2]

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Triglycidylurazol is a teroxirone derivative proposed for clinical trials on the basis of a broad spectrum of activity against murine tumors and a reduced potential for toxic manifestations at the injection site as compared to the parent compound. This phase I trial was designed to define the maximum tolerated dose of triglycidylurazol given by iv bolus on a 5-day schedule. Twenty-eight adult patients with a variety of solid tumors were entered. Their median performance status was 2 (range, 0–3), and most had received prior radiotherapy, chemotherapy, or both. A median of one course (range, one to four) was administered, for a total of 47 courses. Doses were escalated from 6 to 250 mg/m^2/day. Leukopenia and thrombocytopenia were dose-related and -limiting, with a strong suggestion of increased myelosuppression with repeated courses. Nonhematologic toxic effects were generally mild to moderate. Nausea and vomiting were experienced by most patients. Local toxic effects consisting of venous discoloration, phlebitis, and/or sloughing were encountered in about one-half of the patients. Possible drug-related impairments in liver function were noted in three patients. Negligible alopecia and fatigue were also observed. Antitumor effect was detected in one patient with adenocarcinoma of unknown origin. A dose of 200 mg/m^2/day for 5 consecutive days may be recommended for phase II trials. [Cancer Treat Rep 70:599–603, 1986]

Triepoxy derivatives are new chemotypes that are believed to act as alkylating agents (1). Clinical investigations with the lead compound of this series, triglycidyltriazinetrione or teroxirone, revealed dose-limiting thrombophlebitis and skin ulceration at the injection site, which precluded further clinical studies (2,3). These local toxic effects were believed to be related to poor water solubility.

Analogs of teroxirone were screened to identify compounds with higher solubility and similar or better anticancer properties. Triglycidylurazol (TGU; fig 1) exhibits higher stability and water solubility, as compared to the parent compound. Anticancer activity has been demonstrated against a variety of ip implanted murine tumors including the P388 and the L1210 leukemias, as well as the sc implanted B16 melanoma. Significant antitumor efficacy has also been reported against Colon 38 and advanced RC renal carcinomas. In a P388 leukemia subline made resistant to cyclophosphamide, TGU achieved an increase in life span > 200%, with two long-term survivors, while no activity was detected for cyclophosphamide. Against human melanoma xenografts in the subrenal capsule assay, TGU was recently found to be more active than melphalan, dacarbazine, and carmustine (4). In the L1210 leukemia model, no schedule dependency was identified after iv or ip administration. Following single ip administrations in CDF_1 mice, the LD10 and LD50 were 65 and 80 mg/kg, respectively (1). The clinical formulation is a 50:50 mixture of the α and β stereoisomers; these species have comparable physical properties as well as similar antitumor activity.

This phase I study was designed to determine the maximum tolerated dose of TGU when given as an iv bolus daily for 5 consecutive days. This work was undertaken as part of the new drug program of the Early Clinical Trials Group of the European Organization for Research on Treatment of Cancer.

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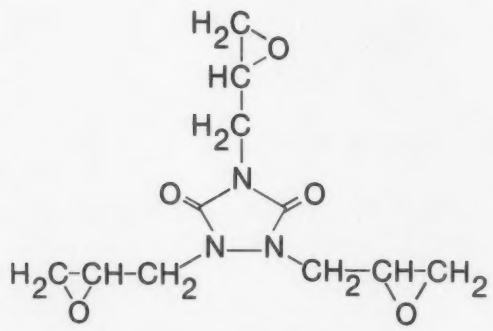

FIGURE 1.—Structure of TGU.

MATERIALS AND METHODS

The study accrued 28 patients with a variety of pathologically documented solid tumors which were not suitable for conventional therapy (table 1). Twelve patients had measurable disease and were evaluated for response. There were 16 men and 12 women, with a median age of 58 yrs (range, 20–77). They were fully or partially ambulatory, with a life expectancy of at least 6 weeks. All patients but three were previously treated with radiotherapy (four patients), chemotherapy (seven patients), or both (14 patients). Two patients had been administered mitomycin and one had received diaziquone. A minimum of 4 weeks had elapsed since prior radiotherapy or chemotherapy. On entry, all patients had wbc count $\geq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, and normal hepatic (bilirubin < 1.5 mg/dl) and renal (serum creatinine ≤ 1.5 mg/dl) functions. Two patients who had serum creatinine levels of 1.9 mg/dl were treated with daily doses of 12 and 24 mg/m^2, respectively, and are reported separately.

TABLE 1.—Patient characteristics

Characteristic	No. of patients*
Eligible	28
Median age in yrs (range): 58 (20–77)	
Median performance status (range): 2 (0–3)	
Male/female	16/12
No prior therapy	3
Prior radiotherapy	4
Prior chemotherapy	7
Prior chemotherapy and radiotherapy	14
Tumor	
Head and neck	5 (1)
Unknown primary site	3 (1)
Uterine cervix	3
Melanoma	3 (3)
Sarcoma	3 (3)
Colon carcinoma	2
Thyroid	2 (2)
Miscellaneous	7 (2)

*Nos. in parentheses = patients with evaluable lesions.

Physical examination, complete history, and SMA-12 serum chemistries were obtained prior to each treatment and repeated every week. Cbcs with differentials were scheduled three times weekly. Other tests were performed as indicated. Responses were assessed according to World Health Organization (WHO) criteria (5).

TGU was supplied by Asta Werke, Bielefelt, Federal Republic of Germany, as a lyophilized dried powder, each vial containing 100 mg of the active compound. The drug was reconstituted in water to a final concentration of 20 mg/ml and administered as an iv bolus followed by a 30-minute infusion of 5% dextrose in water at daily doses up to 96 mg/m^2. Since this procedure resulted in severe local toxic effects, TGU was then reconstituted in normal saline to the same concentration and drug administration was followed by a 30-minute infusion of normal saline. TGU was given daily for 5 consecutive days. The starting dose was 6 mg/m^2/day corresponding to $\frac{1}{10}$ of the LD10 in mice (6). Daily doses were escalated to 175 and 250 mg/m^2. Life-threatening toxic effects at this latter level prompted the exploration of daily doses of 200 mg/m^2 in subsequent entries. Initially, re-treatments were scheduled every 3 weeks; during the trial, this interval was progressively increased to 5–6 weeks to allow for full hematologic recovery. At all but the two highest dose levels, patients were re-entered at a higher level if no hematologic toxic effect was encountered. At each dose level, one to seven new patients were entered and three to 11 courses were administered. Fifteen patients received one course, nine received two courses, two received three courses, and two received four courses, for a total of 47 courses. Antiemetics were not routinely used.

RESULTS

With daily doses of 200 and 250 mg/m^2, follow-up was at least 5 weeks. At lower doses, all patients but two were followed for a minimum of 3 weeks. These two patients received TGU at daily doses of 48 and 175 mg/m^2, respectively. One patient refused follow-up after Day 10 and one died from disease progression on Day 17.

Myelosuppression consisting of leukopenia and thrombocytopenia was clearly dose-related and -limiting, with a steep dose-response relationship. Leukopenia was first noted at doses of 96 mg/m^2/day (table 2). With daily doses of 200 mg/m^2, leukopenia was observed in seven of eight patients and it was mild to moderate in six; at 250 mg/m^2/day, it was severe to life-threatening in all patients. At the highest dose level, one patient died on Day 44 from progressive disease while she had still profound myelosuppression. In

TABLE 2.—Drug-induced leukopenia

Daily dose (mg/m^2)	No. of— Evaluable patients/ courses	No. of— Patients with toxic effects	Median nadir × 10^3 cells/mm^3 (range) Wbc count	Median nadir × 10^3 cells/mm^3 (range) PMN count	Median (range) Day to— Nadir	Median (range) Day to— Recovery
6	3/3	0	5.9 (5.0-10.0)	4.9 (3.6-7.6)		
12	3/4	0	5.8 (5.7-9.5)	4.4 (4.3-6.7)		
24	4/5	0	6.9 (4.7-9.7)	5.1 (4.1-7.8)		
48	4/4	0	7.0 (4.3-8.8)	4.8 (3.3-7.0)		
96	4/4	2	4.8 (3.4-6.5)	4.1 (2.0-5.6)	21 (19-22)	25 (23-26)
175	3/3	2	3.9 (3.2-4.0)	2.5 (1.8-2.6)	18 (17-19)	21 (19-22)
200	8/11	7	3.1 (0.5-5.0)	1.6 (0.2-2.8)	16 (12-27)	35 (17-40)
250	7/11	7	1.0 (0.2-2.0)	0.3 (0.1-1.2)	25 (13-36)	44 (40-87)

most patients, leukopenia started before Day 14 and was often prolonged with a suggestion of a double leukocyte count nadir. At the two highest dose levels, recovery was generally observed during the 5th or the 6th week.

Thrombocytopenia was observed only at the two highest dose levels (table 3). At 200 mg/m^2/day, three patients had a platelet count < 50,000/mm^3, while four had no thrombocytopenia at all. At the highest dose, all patients had severe to life-threatening thrombocytopenia.

Five patients were re-treated at the same dose level and had myelosuppression. One patient received four courses at a daily dose of 200 mg/m^2 and had leukopenia only during the third course. In the other four patients, leukopenia during the second or subsequent courses was progressively more severe and more prolonged, suggesting cumulative myelosuppression. For example, one patient received three courses at a daily dose of 250 mg/m^2. The wbc count nadir decreased progressively from 2500/mm^3 to 2300 and 2000/mm^3. The corresponding figures for the platelet count nadirs were 96,000, 49,000, and 33,000/mm^3. Time to recovery was progressively prolonged from 45 to 87 days.

A wide range of wbc and platelet count nadirs was observed at 200-250 mg/m^2/day (tables 2 and 3). This observation might be related to variations in pretreatment patient characteristics, especially performance status and prior chemotherapy. During the first course at daily doses of 250 mg/m^2, median wbc and platelet count nadirs were 1500 and 39,000/mm^3, respectively, compared to corresponding nadirs of 600 and 13,000/mm^3 for patients with less favorable characteristics.

One patient previously treated with mitomycin experienced life-threatening myelosuppression at daily doses of 250 mg/m^2. She was re-treated at a dose of 200 mg/m^2, resulting in wbc and platelet count nadirs of 1500 and 31,000/mm^3, respectively. Another patient previously treated with mitomycin was entered at this dose level and had no hematotoxicity. Two patients with minor renal alterations received daily doses of 12 and 24 mg/m^2 (not included in tables 2 and 3). One patient experienced transient leukopenia, with a wbc count of 3900/mm^3 on Day 10 and a prompt recovery on Day 13; the other patient showed no toxic effects.

Drug-induced anemia, defined as a drop in hemoglobin level by ≥ 2 g/dl, was detected in six of eight patients at daily doses of 200 mg/m^2 and in all patients at the highest dose level. There were no signs of hemolysis or bleeding. Transfusion was required in seven patients.

Nausea and vomiting was the most common nonhematologic toxic effect (table 4). It was mild to moderate except in three patients who had received prior chemotherapy. Local reactions at the site of injection were less frequent and less severe than those previously observed with teroxirone. Phlebitis and venous discoloration were first noted at daily doses of 12 mg/m^2. At 48 and 96 mg/m^2, two patients experienced erythema on Day 3 that was followed by phlyctena and skin necrosis. Drug reconstitution in saline appeared to reduce the incidence and severity of local effects. At the highest dose level, however, one patient had sloughing during his second course. Repeated injections during the following course produced only minor toxicity. Fatigue, unrelated to anemia, and alopecia were seen occasionally and were generally mild. Bilirubin increase was observed at daily doses > 175 mg/m^2 in three patients apparently free of metastatic liver involvement. This abnormality was minor, rapidly reversible, and not consistently accompanied by an increase in liver enzymes. In one patient, this transient bilirubin increase was seen in two consecutive courses at 175 and 250 mg/m^2. No histologic documentation was obtained to substantiate possible liver toxicity. Serum creatinine elevations were found in two patients who had had prior cisplatin. Two patients previously exposed to vincristine had paresthesia.

No objective response was reported among the 12 patients with measurable disease. Clinical improvement and shrinkage of liver metastases detected by computerized tomographic scan were observed for 9+ months in one patient with carcinoma of unknown origin.

TABLE 3.—Drug-induced thrombocytopenia

Daily dose (mg/m^2)	No. of—		Median platelet count nadir $\times 10^3$ cells/mm^3 (range)	Median (range) Day to—	
	Evaluable patients/ courses	Patients with toxic effects		Nadir	Recovery
6	3/3	0	300 (187-445)		
12	3/4	0	318 (129-341)		
24	4/5	0	137 (106-400)		
48	4/4	0	304 (245-412)		
96	4/4	0	285 (152-613)		
175	3/3	0	113 (105-381)		
200	8/11	4	105 (31-130)	23 (20-24)	33 (26-40)
250	7/11	7	14 (3-43)	22 (17-32)	40 (31-72)

DISCUSSION

The dose-limiting toxic effect of TGU is myelosuppression, which is often prolonged and dose-related with a steep dose-response relationship. At the highest dose level, leukopenia and thrombocytopenia were severe to life-threatening in all patients, whereas, with a 20% lower dose, myelosuppression was generally moderate. In patients receiving two or more courses at toxic dose levels, myelosuppression was more pronounced during the second or subsequent courses and recovery was progressively delayed, suggesting cumulative hematologic toxicity. During the first course at toxic dose levels, a wide variation in leukocyte and granulocyte count nadirs was observed. This observation could be partially related to patient pretreatment characteristics, but firm conclusions would have required larger numbers of patients per dose level. Due to the steep dose-response relationship and the rapidly cumulative myelosuppressive and steep dose-response relationship, doses were not escalated above a daily dose of 250 mg/m^2, which was anticipated to be the maximum tolerated dose for good-risk patients.

Two phase I trials using a single intermittent iv schedule yielded very comparable results (7,8). Myelosuppression was dose-limiting, dose-related, and cumulative. It was also characterized by a steep dose-response relationship. As observed with the daily × 5 schedule, patient characteristics, especially poor performance status and prior chemotherapy, appeared to significantly increase hematologic toxicity.

Overall, TGU was well-tolerated. Nausea and vomiting was experienced by most patients but antiemetics were not commonly required. Severe vomiting was experienced by only three patients. Local toxic effects consisting of phlebitis and venous discoloration were observed at all but two dose levels and were occasionally severe. These effects appeared to be significantly reduced in frequency and severity when the drug was reconstituted in normal saline instead of water. A lower incidence of these toxic effects was also reported after bolus injection as compared to a 30-minute infusion (8). None of the three trials, using single- or repeated-dose administrations, has demonstrated clear dose-effect relationship for local toxicity. Better local tolerance to TGU as compared to teroxirone was noted; whether this is actually related to the higher water solubility of TGU is still speculative. In any event, it remains a significant problem when the drug is given daily for 5 consecutive days, whereas, in the two studies using a single intermittent dose schedule, phlebitis appeared to be negligible.

The trial did not reveal major antitumor activity. However, there was a small number of patients with measurable disease who were adequately treated, and most had been heavily pretreated.

TGU appears to be a potential candidate for phase II study and a dose schedule of 200 mg/m^2/day for 5 con-

TABLE 4.—Nonhematologic toxic effects*

	Daily dose (mg/m^2)							
	6	12	24	48	96	175	200	250
No. of courses	3	4	5	5	4	4	10	11
No. of patients	3	3	4	5	4	4	8	7
No. of patients with toxic effects	0	3	1	3	4	3	7	7
Nausea and Vomiting		2	1	2	3	2 (1)	6 (2)	5
Local		1		2 (1)	2 (1)	1	3	5 (1)
Infection							2	4 (2)
Fatigue		1			1		1 (1)	
Alopecia								2

* Nos. in parentheses = WHO grade III-IV toxicity.

secutive days can be recommended. In view of the steep dose-effect relationship for myelosuppression, lower dosages should be considered with unfavorable pretreatment characteristics. Of note, the higher incidence of local reactions observed with repeated administrations would make the single-dose schedule more attractive for further clinical trials.

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Phase I Trial of Taxol Given as a 3-Hour Infusion Every 21 Days[1,2]

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Taxol is a unique plant product that promotes in vitro assembly of microtubules. In a phase I trial, adults with advanced solid tumors were given taxol (formulated with cremophor EL and dehydrated alcohol) as a 3-hour iv infusion every 21 days. The total dose administered ranged from 15 to 230 mg/m² in nine escalation steps. Leukopenia, thrombocytopenia, nausea and vomiting, alopecia, stomatitis, transient rashes, increases in serum triglyceride levels, and hypersensitivity reactions were observed. Hypersensitivity reactions characterized by acute dyspnea, generalized erythema, and hypotension immediately following the initiation of the taxol infusion occurred in three of five patients receiving ⩾ 190 mg/m² (18% of patients overall). No antitumor activity was observed. Hypersensitivity reactions constituted a treatment-limiting toxicity for this preparation of taxol given on this schedule over the dosage range examined. With the severity and unpredictability of the hypersensitivity reactions, further usage of taxol is not indicated with this drug formulation on this administration schedule. Further studies are warranted to uncover ways to permit the safe administration of taxol. [Cancer Treat Rep 70:605–607, 1986]

Taxol is a novel plant product isolated from the needles and bark of the western yew, *Taxus brevifolia* (1). It (fig 1) is the prototype for a new class of antitumor drugs which are characterized by their capacity to promote the assembly of microtubules. Unlike the vinca alkaloids and colchicine, drugs which inhibit microtubule assembly, taxol promotes the rate, extent, and number of nucleations in the in vitro assembly of tubulin (2). Taxol-treated microtubules resist disassembly by calcium or cold (4 °C), conditions that affect untreated microtubules. In tissue culture, taxol is a potent inhibitor of cell replication in the G_2 or M phase of the cell cycle (3). Cytoplasmic microtubules in these drug-related cells are resistant to disassembly by cold and drugs which inhibit microtubule assembly. In addition, these cells display an unusual interphase microtubule cytoskeleton consisting of free and bundled microtubules and lose their ability to migrate. The molecular pharmacology of taxol has recently been reviewed (4,5).

Preclinical studies have demonstrated taxol to have antitumor activity against the ip implanted B16 melanoma and the human MX-1 mammary tumor xenograft (6). In dogs, myelosuppression, diarrhea, emesis, oligospermia, cellular depletion in lymphoid tissues, changes in serum hepatic enzymes, and elevations in cholesterol and triglycerides were observed (7). The formulation vehicle itself (cremophor EL) produced hypotension in dogs (7). Based on the above, a phase I trial of taxol given as a 3-hour infusion every 21 days was undertaken.

PATIENTS AND METHODS

All patients had histologically documented advanced solid tumors. Each had a Karnofsky performance status ⩾ 50%. No patient had received any radiation therapy or chemotherapy for at least 21 days prior to receiving taxol and for at least 42 days after receiving a nitrosourea or mitomycin. All patients had stable heart rhythm, no clinical congestive heart failure or angina, leukocyte count ⩾ 4000/mm³, platelet count ⩾ 100,000/mm³, serum creatinine ⩽ 1.5 mg/dl, and serum bilirubin ⩽ 1.5 mg/dl.

Taxol was supplied by the National Cancer Institute (Bethesda, MD) as a solution containing 30 mg of the drug in 6 ml of 50% polyoxyethylated castor oil (cremophor EL) and dehydrated alcohol, USP 50%. For each patient, the appropriate dose of taxol was diluted to

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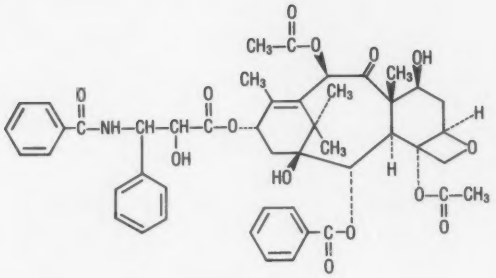

FIGURE 1.—Structure of taxol.

a total volume of 500 ml with 0.9% sodium chloride injection, USP, and infused over 3 hours through an in-line filter (IVEX-2, Abbott Laboratories, 0.2 μm). Courses were repeated every 21 days. An adequate cycle of therapy was defined as a single infusion of taxol and a 21-day observation period. The trial was initiated at a dose of 15 mg/m^2. Escalation proceeded using doses of 30, 45, 75, 100, 135, 160, 190, and 230 mg/m^2. Three patients were entered at each dosage level. A fourth patient was added at the 160-mg/m^2 level. Patients who experienced no drug-related toxicity were eligible to re-enter the study at a higher dosage level, but no level was completed solely with patients who had already received taxol. Standard response criteria were used (7).

Prior to the start of therapy, all patients had complete history and physical examination, cbc with platelet count, prothrombin and partial thromboplastin times, serum creatinine, and 12-channel biochemical profile. Fasting glucose, cholesterol, and triglyceride levels were determined before and 24 hours after each dose. Interval studies were repeated 7, 14, and 21 days after the infusion. Assessments of antitumor response were made every 21 days.

RESULTS

Twenty-eight infusions of taxol were administered to 17 patients. Nine patients received one infusion; six, two; one, three; and one, four. All patients completed their planned infusion of taxol and 21-day follow-up except the three patients (11% of courses) who experienced hypersensitivity reactions (described below). The median age of patients was 58 years (range, 44–73). There were 11 men and six women. The Karnofsky performance status was 50%, 60%, or 70% in 12 patients and 80%, 90%, or 100% in five. Prior treatment included chemotherapy (seven patients), radiotherapy (one), chemotherapy and radiotherapy (eight), and none (one). Thirteen patients had non-small cell lung cancer, two had renal cell carcinoma, one had adenocarcinoma of unknown primary site, and one had epidermoid carcinoma of unknown primary site.

Leukocyte count nadirs < 4000/mm^3 (range, 1000–3900) were observed on Day 7 (two courses) or on Day 14 (five courses) in 44% of the courses ⩾ 75 mg/m^2. Platelet counts < 150,000/mm^3 (range, 80,000–130,000) were noted on Day 7 or Day 14 in 23% of the courses ⩾ 100 mg/m^2. Recovery of platelet and leukocyte counts occurred in all patients by Day 21. The median hemoglobin decrease per dosage level ranged from 0.3 g (30-mg/m^2 level) to 2.5 g (135-mg/m^2 level). There was a significant increase in mean serum triglyceride levels when fasting pretreatment values (172 mg/ml) were compared to fasting values the morning following therapy (216 mg/dl; $P = 0.002$; paired t test). Mean serum cholesterol values were slightly increased (203 versus 210 mg/dl; $P = 0.09$; paired t test).

Mild to moderate nausea or emesis was noted in 36% of courses and hair loss was seen in 32%. Moderate stomatitis was noted in one patient at the 135-mg/m^2 dose level on Day 7 and mild, transient rashes were noted in two patients at the 15-mg/m^2 level within 24 hours of taxol infusion.

Treatment-limiting hypersensitivity reactions were seen in three of five patients (60%) treated with ⩾ 190 mg/m^2 of taxol and are described in table 1. Within 5 minutes after the start of the taxol infusion, all three patients noted generalized warmth, erythema, and dyspnea. Only one patient had a history of allergy of any kind. The patient had developed urticaria following an infusion of elipticinium. Prior to this trial, none of these

TABLE 1.—Hypersensitivity reactions following taxol administration

	Patient No.—		
	1	2	3
Age (yrs)	48	72	46
Sex	M	F	M
Performance status (%)	80	60	80
Dose level (mg/m^2)	190	190	230
Prior taxol	No	No	Yes (190 mg/m^2)
Onset after start of infusion (mins)	5	5	5
Total dose (mg) of taxol given	8	6	2.5
Concentration of taxol solution (mg/ml)	0.7	0.6	1.1
Symptoms and signs			
Erythema	Yes	Yes	Yes
Dyspnea	Yes	Yes	Yes
Nausea	Yes	No	No
Abdominal pain	No	No	Yes
Wheezing	No	No	No
Rash	No	No	No
Hypotension	No	No	Yes
Outcome	Resolved over 15 mins	Resolved over 40 mins	Asystole, death

patients had received cremophor-containing medications at our institution. These drug reactions resolved within 40 minutes in Patients 1 and 2. Both patients received diphenhydramine (50 mg iv) after the reaction occurred and neither received further taxol. Patient 3 developed hypotension and asystole that progressed to electromechanical dissociation and death despite maximal resuscitation efforts, including cardiopulmonary resuscitation (beginning within 1 minute after the onset of the reaction); the administration of epinephrine, isoproterenol, dopamine, calcium, diphenhydramine, and methylprednisolone; pacemaker insertion; and endotracheal intubation.

There were no objective antitumor responses observed following the 23 adequate treatment courses in 16 patients with evaluable indicator lesions.

DISCUSSION

Taxol was selected for clinical investigation because of its unique structure and mechanism of action as well as its demonstrated anticancer effects in both a murine tumor and human tumor xenograft. When given as a 3-hour infusion at doses up to 190 mg/m^2 every 21 days, leukopenia, thrombocytopenia, nausea and vomiting, alopecia, stomatitis, transient rashes, and hypersensitivity reactions were observed. No anticancer effects were noted in this trial.

Hypersensitivity reactions characterized by acute dyspnea and erythema following the infusion of from 2.5 to 8 mg of taxol occurred in 60% (three of five) of the patients receiving $\geq$ 190 mg/m^2 of the drug and in 18% (three of 17) of the patients overall, with one episode leading to irreversible hypotension. Similar reactions have been associated with other drugs formulated with the nonionic surfactant cremophor (8,9). This present formulation of taxol contains the highest concentration of cremophor per unit of drug and per phase II dose of any chemotherapeutic agent clinically tested to date (8). Although reactions to the cremophor vehicle are the most likely cause of the hypersensitivity symptoms, the complex of taxol plus cremophor or the taxol molecule itself must still be considered possible causes for the syndrome. Reactions occurred in patients who both had and had not received taxol previously. It is not known whether these reactions represent true anaphylactic (mediated by preformed IgE or IgG4) or anaphylactoid (nonimmunologic reactions like those seen with radiocontrast injections) phenomena. Although similar reactions were observed at other institutions following the administration of lower planned doses of taxol on this schedule (8,10), no reactions were observed prior to the 190-mg/m^2 dose level in this trial, suggesting a possible dose- or concentration-related effect.

Hypersensitivity reactions constitute a severe and unpredictable treatment-limiting toxicity for the present cremophor-containing formulation of taxol given on this schedule. Further studies are needed to see if pretreatment regimens, alternative schedules (11,12), or a reformulated preparation will permit the safe administration of this compound.

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Phase I Trial of Recombinant Interferon Gamma by 1-Hour Iv Infusion[1,2]

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Fifteen patients with advanced malignancy were treated with recombinant interferon gamma (rIFN-γ) (specific activity ~ 2 × 10^7 units/mg, purity > 99%) given by 1-hour iv infusion three times a week for 6 weeks, at fixed dose levels of 0.1, 0.5, 1.0, or 2.0 mg/m^2/day. The common side effects were constitutional symptoms, including fever, chills, myalgias, and headache, but these were less severe than those observed following daily 6-hour iv infusions. Significant changes in blood cell counts and routine serum chemistries were not observed, but there was a dose-dependent increase in serum triglyceride levels. The maximum safely tolerated dose achieved was 1.0 mg/m^2/day. Peak serum interferon levels occurred at the midpoint of the infusion and were dose-dependent. rIFN-γ was rapidly cleared from serum and no detectable activity was found 2 hours after the infusion. Two patients, both with B-cell malignancies, showed objective evidence of tumor regression during the treatment. Treatment was associated with an increase in serum levels of β_2-microglobulin and the H_2O_2 secretory capacity of peripheral blood monocytes. We conclude that rIFN-γ administered by short iv infusion can induce biological activities and causes less toxicity than when given by prolonged iv infusion. [Cancer Treat Rep 70:609–614, 1986]

Gamma interferon (IFN-γ) is a T-cell-derived cytokine that shares many of the properties of IFN-α and -β. However, it is unique in that it has shown greater antiproliferative activity (1–3), more potent stimulation of macrophage activity (4,5), and distinct effects on cellular differentiation (6–8). In vitro studies suggest that IFN-γ activates cells more slowly than IFN-α and -β (9), and that it binds to a distinct cellular receptor (10).

Preliminary phase I studies with partially purified human IFN-γ suggested that repetitive dosing and prolonged infusions were required to induce consistent biological effects (11,12). Based on these observations, we conducted a phase I trial of rIFN-γ given by daily 6-hour iv infusion (8). This treatment induced antitumor activity and a range of biological activities including increases in serum levels of β_2-microglobulin, H_2O_2 secretion by monocytes, and maturation of cells of myeloid and B-cell lineage. However, patients in this study experienced substantial toxicity and required long periods of confinement to the hospital for iv infusions.

To find a treatment schedule which is better tolerated and, at the same time, induces similar effects on the immune system and on tumor growth, we have conducted a phase I trial of rIFN-γ given by short intermittent iv infusions. We describe here the toxicity, therapeutic effects, serum IFN levels, and effects on immune function of 1-hour iv infusions of rIFN-γ given three times per week.

MATERIALS AND METHODS

Patient Selection

All patients had histologically proven advanced malignancy. Patients were eligible for the study if they were

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ambulatory, had a Karnofsky performance status ≥ 50%, and had a minimum life expectancy of 12 weeks. Preserved renal function (serum creatinine ≤ 2.0 mg/100 ml and ≤ 2+ proteinuria), hepatic function (bilirubin ≤ 1.5 mg/100 ml and prothrombin time ≤ 1.3 times control), and hematologic function (wbc count ≥ 4000/mm^3; granulocyte count ≥ 2000/mm^3; and platelet count ≥ 100,000/mm^3) were also required. Written informed consent was obtained from all patients prior to participation in the study. No patient had received anticancer therapy for at least 4 weeks prior to entry in this trial.

Patients were evaluated prior to treatment with a history and physical examination, cbc, serum biochemical profile, urinalysis, and prothrombin time. These tests were repeated two times in the first week and at least once a week thereafter during treatment. All patients had chest x-ray and ECG prior to and at the completion of the study.

Interferon

rIFN-γ was prepared from *Escherichia coli* and provided by Genentech, Inc (South San Francisco, CA) (8). The specific activity of this material was ∼ 2 × 10^7 units/mg of protein and it was > 99% pure.

Study Design

Patients were treated at fixed dose levels of 0.1, 0.5, 1.0, or 2.0 mg/m^2/day (corresponding to approximately 2, 10, 20, and 40 × 10^6 units/m^2/day) administered by 1-hour iv infusion on alternate days three times per week × 6 weeks. After four patients were treated at a given dose level without unacceptable toxicity, the next group of patients was treated at the next higher dose level. Patients showing objective evidence of tumor regression or stable disease were treated with rIFN-γ at the original dosage, three times per week im until there was evidence of disease progression.

Tumor response was evaluated by physical examination and appropriate laboratory and radiological studies. Responses were graded according to standard criteria as described earlier (8).

Pharmacokinetic Studies

Serum IFN levels were measured in two patients treated at each dose level before the infusion and at the following time points: ¼, 1, 1½, 2, 2½, 3, 5, 7, and 24 hours after the start of the 1-hour infusion on the first day of treatment. Serum IFN levels were measured by a standard enzyme-linked immunosorbent assay (ELISA). The assay sensitivity was ≥ 0.4 ng/ml of serum. In addition, sera from patients were also tested for neutralizing antibodies to IFN-γ prior to, immediately after completion of, and 4 weeks after completion of the study as previously described (8).

Immunologic Profile

The effects of rIFN-γ treatment on H_2O_2 secretory capacity of peripheral blood monocytes were monitored in several patients, immediately prior to the first infusion and immediately after the first infusion and on the next two mornings (24 and 48 hours after the first infusion) before the second treatment (13).

Serum levels of β_2-microglobulin were monitored in all patients during therapy with rIFN-γ as described previously (8).

RESULTS

Patient Characteristics

Fifteen patients were entered in this study; eight were males and seven were females. The median age was 37 years (range, 22–70) and the median performance status was 80% (range, 70%–90%). Two-thirds of the patients had received prior chemotherapy, but only one had been treated previously with alpha interferon. The diagnoses included malignant melanoma (three patients), medullary carcinoma of the thyroid (two), Hodgkin's disease (two), nodular poorly differentiated lymphocytic lymphoma (four), diffuse poorly differentiated lymphocytic lymphoma (one), B-cell lymphoblastic lymphoma (one), chronic myelogenous leukemia (one), and Kaposi's sarcoma associated with the acquired immunodeficiency syndrome (one).

Toxicity (table 1)

Side effects commonly observed with rIFN-γ were qualitatively similar to those seen with other IFN species and included fever, chills, fatigue, myalgias, headache, nausea, anorexia, and occasional vomiting. In general, these side effects were considerably less intense than those reported earlier for rIFN-γ given by prolonged iv infusion (8). The peak of the febrile response occurred during the first week of treatment in most of the patients. The number of patients experiencing temperatures > 39°C was higher at dose levels ≥ 0.5 mg/m^2 than at a dose of 0.1 mg/m^2. Fatigue was not profound and did not lead to a significant decrease in performance status. No significant weight loss occurred during the treatment period.

Dose-Limiting Toxic Effects

Fourteen of 15 patients completed 6 weeks of therapy; 13 at the original dose level and one at a reduced dose. One patient at the 0.5-mg/m^2 dose level did not receive the last 3 weeks of treatment because of disease progression. No dose-limiting toxic effects were seen at the two lower dose levels (≤ 0.5 mg/m^2). At a dose of 1.0 mg/m^2 patients experienced more constitutional symptoms in-

cluding fever > 39°C (three patients), severe headache requiring analgesics (three), and transient orthostatic hypotension and light-headedness (two) in the absence of apparent hypovolemia. At the highest dose (2 mg/m^2), the only patient entered, a 27-year-old man with chronic myelogenous leukemia, experienced chest discomfort about 12 hours after the first infusion. This was described by the patient as foreign-body sensation in the retrosternal area and was accompanied by mild shortness of breath. This subsided in a few minutes to be followed by left shoulder pain which resolved promptly after administration of acetaminophen. An ECG revealed slight prolongation of the PR interval compared to pretreatment (0.17–0.2 seconds), but the clinical findings, chest x-ray, blood gases, cardiac enzymes, and heart scan were unremarkable. A subsequent dose reduction to 1 mg/m^2 was better tolerated and similar symptoms did not occur. No additional patients were entered at this dose level since the nature of this episode was unclear. Since patients experienced moderate but manageable toxicity at the 1-mg/m^2 dose level, we consider it a safely tolerated dose using this route and schedule of administration.

Effects on Blood Cell Counts

Minor decreases in wbc and neutrophil counts were seen by the end of the first week of treatment, but recovery was rapid and was evident by the beginning of the second week. No patient developed significant leukopenia (wbc count < 2000/mm^3), neutropenia (polymorphonuclear neutrophil count < 1000/mm^3), or thrombocytopenia (platelet count < 100,000/mm^3). No episode of sepsis or serious infection occurred during treatment. There were no significant changes in lymphocyte count, monocyte count, or hematocrit values.

Effects on Serum Chemistries

The only significant change in blood chemistry values was an increase in serum triglyceride levels (table 2). Triglyceride levels were determined prior to the first treatment and at weekly intervals throughout the 6-week treatment course. Samples were drawn in the morning prior to treatment, but were not uniformly obtained after an overnight fast. Mean serum triglyceride levels at each time point for all patients are shown in table 2. Of 80 determinations made during treatment (two to six values per patient; median, six), 70 were greater than the pretreatment value for that patient. Of the ten that were less than the pretreatment value, eight were in patients treated at a dose of 0.1 mg/m^2. Within each dose level, mean triglyceride values at each time point were also compared with the pretreatment mean for that dose using the paired t test. At the lowest dose level (0.1 mg/m^2), none of the posttreatment means was significantly elevated above the baseline. At a dose of 0.5 mg/m^2, significant differences ($P < 0.05$) were observed on Days 15 and 22. At the highest dose (1.0 mg/m^2), significant increases were observed at all time points with the exception of Day 15. Lipoprotein electrophoresis was carried out in a few patients and revealed an increase in very low density lipoproteins (VLDL). There was no concomitant elevation of serum cholesterol.

No renal, hepatic, or neurologic toxicity was seen.

Pharmacokinetic Studies

Mean serum IFN levels on Day 1 are plotted against time (fig 1) for two patients at each of the first three dose levels and the single patient treated at 2.0 mg/m^2. At a dose of 0.1 mg/m^2, values just above the limit of assay sensitivity were recorded. At doses ≥ 0.5 mg/m^2, peak serum IFN levels occurred at 30 minutes during infusion and were dose-dependent. rIFN-γ was rapidly cleared from the circulation and no detectable activity was found in the serum 2 hours after the infusion. Although the half-life of rIFN-γ could not be calculated given the small number of patients studied, our data are consistent with those of Kurzrock et al (14), who found a half-life of 25–35 minutes after iv bolus injection. No neutralizing antibodies to rIFN-γ were detected in patient serum at any time before, during, or after treatment.

Antitumor Response (table 3)

Seven patients showed stable disease and five had disease progression during treatment. Partial responses were seen in two patients, one with stage IV nodular poorly differentiated lymphocytic lymphoma treated at a dose of 0.5 mg/m^2 and another with lymphoblastic

TABLE 1.—Toxic effects associated with rIFN-γ

rIFN-γ dose (mg/m^2)	No. of patients	Toxic effect*								
		Fever	Chills	Fatigue	Myalgias	Headache	Nausea/ vomiting	Anorexia	Orthostatic hypotension	Light-headedness
0.1	4	4	4	3	4	4(1)	1	—	—	1
0.5	5	5(3)	5	3	3	3(1)	3	2	1	1
1.0	5	5(3)	5	5	5	5(3)	1	1	2	2
2.0	1†	1	1	1	1(1)	—	—	—	—	—

* Nos. in parentheses indicate No. of patients in whom side effects were severe.
†One patient entered at this dose level required dose reduction to 1.0 mg/m^2.

TABLE 2.—Changes in serum triglyceride levels

	No. of patients	Serum triglyceride levels (mg/dl)*		
		Mean ± SE	Range	*P* value†
Pretreatment	15	118.4 ± 14.2	40-195	—
Day 8	12	138.2 ± 17.4	54-212	0.008
Day 15	14	160.9 ± 17.3	64-263	0.003
Day 22	13	179.2 ± 22.8	79-386	0.001
Day 29	14	160.9 ± 18.5	53-280	< 0.001
Day 36	13	173.5 ± 20.0	81-303	0.001
Day 43	14	160.6 ± 25.6	56-392	0.051

* Normal range, 50-160 mg/dl.
†By paired t test with comparison to pretreatment values.

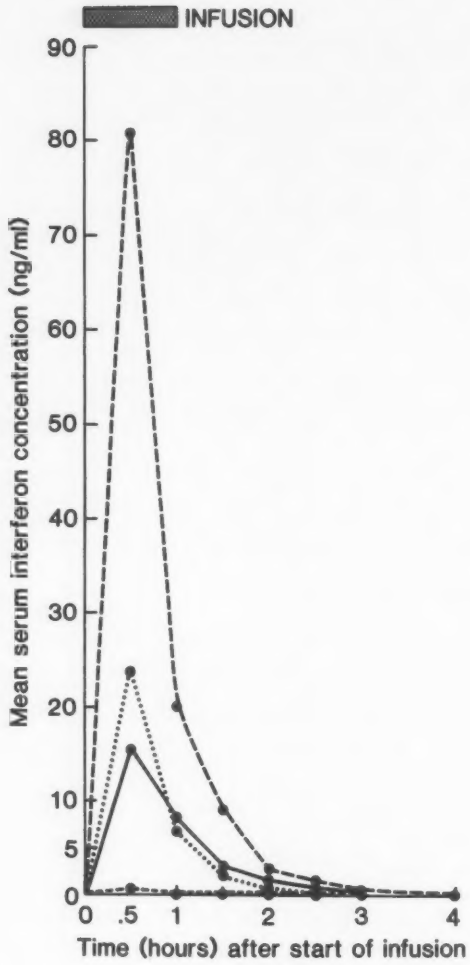

FIGURE 1.—Mean serum IFN levels. ------ = 0.1 mg/m²; —— = 0.5 mg/m²; ····· = 1.0 mg/m²; and ——— = 2.0 mg/m².

lymphoma treated at a dose of 1.0 mg/m². The patient with nodular poorly differentiated lymphocytic lymphoma was previously untreated and had extensive retroperitoneal and pelvic nodal disease and focal bone marrow involvement. Treatment with rIFN-γ led to a decrease in lymph node size by 70%-80%. The response is still maintained at 27 weeks on im therapy three times per week.

The patient with lymphoblastic lymphoma was heavily pretreated with chemotherapy and had bone marrow involvement as the only site of measurable disease. Lymphocyte marker studies performed before treatment with rIFN-γ revealed B-cell phenotype with bright immunofluorescence for surface immunoglobulins. Prior to treatment, the percentage of blasts in the bone marrow was as high as 38% in certain areas. Treatment with rIFN-γ was associated with a decrease in the percentage of blasts from 3% to 7% on repeated bone marrow aspirate. At the same time, a change in phenotype of leukemic cells in the blood and marrow was seen, consisting of a decrease in the expression of surface immunoglobulins, expression of cytoplasmic immunoglobulins, and an increase in the proportion of cells expressing antigens characteristic of mature B cells, including BL3 (A. Al-Katib et al, manuscript in preparation). The response in this patient is maintained at 22 weeks on im therapy three times per week.

In addition, one patient with stage IV nodular poorly differentiated lymphocytic lymphoma had a mixed response to therapy. Treatment with 0.1 mg/m² of rIFN-γ induced a decrease in the size of inguinal lymph nodes (the only measurable disease) by > 50%. Although the decrease in lymph node size was maintained, treatment was discontinued after 11 weeks because of a progressive decline in wbc and platelet counts, suggesting progressive disease in the bone marrow. The patient declined to have a bone marrow aspirate and biopsy, so the degree of marrow involvement could not be confirmed.

Immunologic Effects

H_2O_2 secretion by monocytes.—A complete analysis of these data is a subject of a separate report (15). Six pa-

TABLE 3.—Patient status

rIFN-γ dose (mg/m^2)	No. of patients	Patients completing 6 wks of treatment at—		Response	
		Same dose	Reduced dose	Type	No.
0.1	4	4		Mixed	1
				Stable disease	2
				Disease progression	1
0.5	5	4*		Partial response	1
				Stable disease	3
				Disease progression	1
1.0	5	5		Partial response	1
				Stable disease	1
				Disease progression	3
2.0	1†		1	Stable disease	1

* One patient taken off study after 3 wks of treatment, for disease progression.

†First patient entered at this dose level experienced unacceptable toxicity and required reduction to 1.0 mg/m^2

tients were tested at various time points during treatment. Treatment with rIFN-γ was associated with an increase in the H_2O_2 secretory capacity of monocytes in response to the stimulus phorbol myristate acetate. When tested immediately after adherence to the vessel or after culture for 1 or 2 days before assay, the H_2O_2 secretory capacity increased, ranging from 1.3 ± 0.2-fold to 2.5 ± 0.9-fold above pretreatment values in monocytes drawn 1 or 2 days after the first infusion (16). In addition, morphological changes of monocytes were seen in a few patients. These consisted of enlargement and vacuolization of cells.

Serum β_2-microglobulin.—Serum levels of β_2-microglobulin prior to therapy are plotted against levels after therapy on Day 5 (fig 2). Thirteen of 15 subjects showed an increase in serum levels of β_2-microglobulin at some time during therapy. However, the increases were of lesser magnitude than those observed for patients receiving rIFN-γ by prolonged infusions (8), and the magnitude of the increase was not clearly related to the interferon dose.

DISCUSSION

This study was designed to evaluate the toxicity and biological activities of rIFN-γ given by short, intermittent iv infusion and to compare the results with those obtained using longer and more frequent infusions. A well-tolerated dose of 1 mg/m^2 is twice the maximally tolerated dose observed in our study using daily 6-hour infusions (8).

Even at a dose of 1 mg/m^2, the severity of constitutional side effects was less than that seen at a dose of 0.5 mg/m^2 by 6-hour infusion. It is conceivable that even higher doses might be tolerated by many patients. However, the unexplained episode of chest discomfort in the single patient treated at a dose of 2 mg/m^2, together with prolongation of the PR interval, led us to discontinue dose escalation until the potential effects of rIFN-γ on the cardiovascular system could be clarified. In addition to the above episode, three patients experienced otherwise unexplained orthostatic hypotension. Similar effects on the PR interval and blood pressure were also observed in our 6-hour infusion study (8). In the latter study, however, hypotension was generally associated with high fever and volume depletion. The mechanism by which rIFN-γ may affect the cardiovascular system is unclear. Using rat IFN-α/-β, a decrease in rat myocardial cell-beating rate in vitro has been reported (17). Similar studies with IFN-γ would require supplies of rat IFN-γ, which have, until recently, not been available.

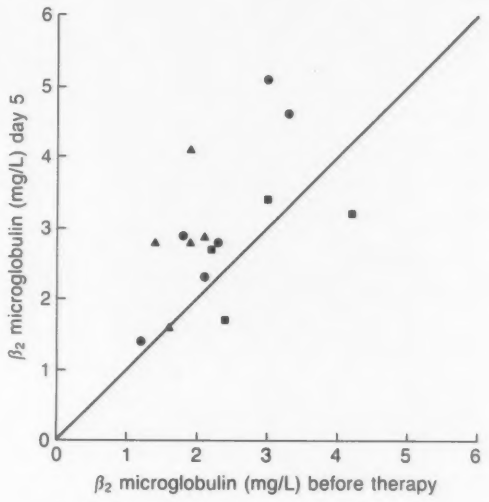

FIGURE 2.—Effect of rIFN-γ treatment on serum β_2-microglobulin levels. ■ = 0.1 mg/m^2; ▲ = 0.5 mg/m^2; and ● = 1.0 mg/m^2.

Unlike prolonged infusions of recombinant or partially purified IFN-γ (8,12), but like iv bolus injection of partially purified IFN-γ (12), short infusions of rIFN-γ produced no dose-limiting myelotoxicity. Similarly, no significant or dose-limiting changes in serum chemistries were induced. The only exception was a dose-related increase in serum triglyceride levels, characterized by high levels of VLDL. The mechanism of triglyceride elevation is not clear. Recent studies have shown that the hyperlipidemia associated with endotoxinemia is mediated by an endotoxin-induced macrophage product (18,19), which markedly suppresses the activity of lipoprotein lipase. This results in accumulation of VLDL and hypertriglyceridemia. It is possible that rIFN-γ induces similar changes by activating macrophages which then release an inhibitor of lipoprotein lipase.

Another macrophage function, the ability to secrete H_2O_2 when stimulated in vitro with phorbol myristate acetate, was increased during treatment with rIFN-γ. Over the dose range tested, the increase in H_2O_2 secretory capacity of peripheral blood monocytes did not vary, a finding similar to that observed after 6-hour infusions over an identical dose range (8). Although the relationship, if any, of the generation of reactive oxygen intermediates to IFN-γ's antitumor effects is not known, the lack of a dose-response relationship for this interferon-induced effect raises questions about the choice of "optimal" doses and treatment schedules for further therapeutic trials. Furthermore, in a series of phase I trials of rIFN-γ, antitumor activity has been documented using both short and long infusion (8), continuous infusion, and daily im injection (J. U. Gutterman, personal communication). It may be that the optimal dose, schedule, and route of administration for rIFN-γ may vary depending on the disease or tumor type for which it is intended. For the treatment or prophylaxis of certain chronic infections in which a rationale for macrophage activation exists (eg, lepromatous leprosy or certain infections associated with the acquired immunodeficiency syndrome), lower doses, short infusions, and less frequent administration, which do not induce sustained serum interferon levels, may be sufficient to induce the desired effects while avoiding the toxicity of high daily doses and prolonged infusions. For the treatment of certain tumors, however, there may be a rationale for higher doses, frequent administration, and prolonged infusion times which maintain consistent levels of serum IFN. The superiority of one approach over another for a given disease will need to be established in prospective phase II and III trials.

Recent in vitro studies have shown synergistic antiproliferative effects when rIFN-γ was used in combination with rIFN-α or -β (20) and recombinant-DNA-produced tumor necrosis factor (21). The schedule of administration for rIFN-γ described here, which is well-tolerated and induces a range of characteristic biological activities, should be appropriate for trials of such combinations in man.

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Phase II Study of Low-Dose Methotrexate in Advanced Osteosarcoma Followed by Escalation After Disease Progression: A Study of the Soft Tissue and Bone Sarcoma Group of the European Organization for Research on Treatment of Cancer[1]

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Twenty-seven patients with osteosarcoma and measurable metastases were treated with low-dose methotrexate (LDMTX) (80 mg/m^2), followed by high-dose methotrexate (HDMTX) (7.5 g/m^2) after disease progression in 14 patients. LDMTX was administered on Days 1, 8, and 15; if response or stable disease occurred, it was repeated on Days 29 and 43. If response occurred by Day 57, LDMTX was continued every 2 weeks until disease progression. If stable disease occurred by Day 57, the patient crossed over (optional) to HDMTX. HDMTX was given weekly during the first 3 weeks and continued once every 14 days until disease progression. Twenty-five of the patients were evaluable for response. Three patients (12%) achieved complete remission, with durations of 5, 14, and 34 weeks, respectively. The time to disease progression from the start of treatment was 19, 28, and 42 weeks. Twelve patients (48%) had stable disease, with a median duration of 7.5 weeks (range, 6–20). Ten patients (40%) had disease progression. In general, toxicity with LDMTX was mild. The most frequent toxic effect was stomatitis. Twelve of 14 patients who crossed over to HDMTX were evaluated for response. Six patients had stable disease and six had disease progression. We conclude that the results achieved with LDMTX seem inferior to the results achieved with HDMTX described in the literature. [Cancer Treat Rep 70:615–618, 1986]

The treatment of advanced osteogenic sarcoma with combination chemotherapy is widely employed. The drug most frequently applied is methotrexate (MTX). Data about single-agent activity of this drug are scarce. Jaffe et al (1-3) reported on the efficacy of high-dose MTX (HDMTX) with leucovorin rescue in the treatment of patients with metastatic osteogenic sarcoma. The impetus for these studies was provided by reports from Djerassi et al (4) documenting favorable responses with this treatment in primary cancer of the lung. The rationale for this therapy has been to enhance the intracellular concentration of the drug while preventing excessive toxicity to most tissues by the use of leucovorin.

Although HDMTX-leucovorin undoubtedly has activity in metastatic osteosarcoma, comparatively few patients have been treated with this drug alone and it has not been clearly documented that low doses of MTX are less effective. Notwithstanding, HDMTX-leucovorin is used extensively in combination chemotherapy and in adjuvant programs for osteosarcoma with occasional severe toxicity and at considerable expense.

In view of these data, in 1979 the Soft Tissue and Bone Sarcoma Group of the European Organization for Research on Treatment of Cancer started a prospective randomized trial using low-dose MTX (LDMTX) versus HDMTX in this tumor. In addition, by crossing over at disease progression from LDMTX to HDMTX, we wanted to investigate the hypothesis that drug resistance to MTX is relative and can be overcome by escalating the dose. However, because of very low accrual, the randomization into the HDMTX arm had to stop

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and we decided to continue the study as a single phase II study of LDMTX followed optionally by escalation if disease progression occurred.

MATERIALS AND METHODS

Patients 5–50 years of age with advanced measurable histologically confirmed osteosarcoma and a Karnofsky performance status > 50 were eligible for the study. In addition, no previous therapy with MTX within the last 6 months or other cytotoxic agents within the last 4 weeks and a normal hematologic status and kidney function were required. Responses were determined by x-ray of the chest (posteroanterior and lateral) and, in case of doubt, by tomography.

Treatment

The LDMTX chemotherapy schedule consisted of 80 mg/m^2 given iv on Days 1, 8, and 15. This dose was chosen because it is the highest dose of MTX which can be given without leucovorin rescue. If response or stable disease occurred, two additional doses were given on Days 29 and 43. If stable disease occurred by Day 57, the patient crossed over (optional) to HDMTX. If response occurred by Day 57, LDMTX was continued every 2 weeks until disease progression. Alkalinization of the urine and leucovorin were not instituted in this low-dose regimen.

After institution of adequate diuresis and alkalinization of the urine, HDMTX (7.5 g/m^2) was given in 1000 ml of 50% dextrose as a 6-hour infusion. The leucovorin rescue (15 mg/m^2) was started 2 hours after the termination of the MTX infusion. The first dose was administered iv; thereafter, doses were administered orally at 15 mg/m^2 every 6 hours for a total number of 16 doses. If the MTX level was $> 10^{-6}$ M at 48 hours after the initiation of HDMTX, the patient was given additional leucovorin. Diuresis and alkalinization were maintained at least 48 hours after the end of the HDMTX infusion. HDMTX was given every week during the first 3 weeks. If stable disease or response occurred, HDMTX was continued once every 14 days until disease progression.

Drug administration was postponed for a maximum of 1 week if the leukocyte count was $< 3 \times 10^9$/L and/or the thrombocyte count was $< 100 \times 10^9$/L at Day 8 or 15. A similar adjustment was applied when the drug was given every 2 weeks. The therapy also had to be postponed for a maximum of 1 week in the event of severe mucositis, liver toxicity, or nephrotoxicity (creatinine clearance < 80 ml/min). If postponement for > 1 week was necessary, the patient was considered as a failure due to toxicity. There was no dose adjustment.

Criteria of Evaluation

Patients were considered evaluable if they were treated with a minimum of three courses of LDMTX. Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of 3 weeks. Partial response (PR) was defined as a decrease in size by ⩾ 50% of the sum of the products of the two largest perpendicular diameters of all measurable lesions. Stable disease was defined as either no regression reaching 50% or no increase > 25% in any lesion and no new metastases. Disease progression was defined as a > 25% increase in any lesion or a new metastasis. Toxicity was assessed using the following grading system: grade 0, no toxicity; grade 1, mild toxicity; grade 2, moderate toxicity; and grade 3, severe toxicity.

RESULTS

Between January 1979 and March 1984, 27 patients were entered in the study. Two patients were not evaluable because inadequate drug dosage was given. The ages of the evaluable patients ranged from 13 to 57 years (median, 17). There were 21 men and four women. The median Karnofsky score was 90 (range, 60–100). Twenty-three patients had lung metastases, one had lung and soft tissue metastases, and another had subcutaneous and lymph node metastases. The site of the primary lesion was in the femur (15 patients), tibia (seven), humerus (two), and radius (one). Of the 25 evaluable patients, 19 had surgical resection of the primary tumors: five patients had amputation through the involved bone, 13 had an amputation through the proximal bone or exarticulation, and one had a local resection. Six patients underwent no resection. In three patients, a thoracotomy was previously performed for resection of metastases. Four patients had previously received chemotherapy. One patient had received doxorubicin as adjuvant treatment. Ten months later, metastases appeared and the patient entered the study. Two patients, who already had metastases at the time of presentation, had been treated without success with a combination of doxorubicin and cisplatin and were treated subsequently with MTX. One patient had received three cycles of doxorubicin and cisplatin as primary treatment followed by surgical resection and another three cycles. During the follow-up, metastases developed and the patient was treated with MTX. Eight patients had received prior radiation therapy (three to the primary tumor and four to the lungs as an adjuvant to prevent lung metastases, and one to the primary tumor as an adjuvant to the lungs).

Of the 25 evaluable patients treated with LDMTX, three (12%) achieved CR. The duration of response was 5, 14, and 34 weeks. The time to disease progression

from the start of treatment was 19, 28, and 42 weeks. Twelve patients (48%) had stable disease; however, the median duration was only 7.5 weeks (range, 6-20). Ten patients (40%) had disease progression. Three of four patients who had received prior chemotherapy had stable disease and one had disease progression. Of 25 patients treated with LDMTX, 14 crossed over to HDMTX; 12 of the 14 were evaluable for response. Two patients were not evaluable because one received one cycle and the other received two cycles. In the evaluable patients, no responses were observed. Six patients had stable disease and six had disease progression. The median duration of the stable disease period was 10 weeks (range, 5-19).

Before stopping the randomization between LDMTX/HDMTX, five patients were treated initially with HDMTX. The responses in this very small group of patients, in which two patients had previously received chemotherapy, were as follows: one patient had a CR, one had a PR, and three had disease progression.

Toxicity

In the LDMTX group, the number of courses given per patient varied from three to 22, with a median of 4.7 cycles. In four patients the treatment had to be postponed due to leukopenia ($< 3 \times 10^9$ cells/L) and in three patients due to mucositis. A summary of the nonhematologic toxic effects is given in table 1. Neurological side effects included dizziness and headache.

DISCUSSION

Following the demonstration of the therapeutic efficacy of HDMTX (1,2,5,6) for the treatment of pulmonary metastases of osteosarcoma, this method of administration had been adopted as single- and multiple-agent adjuvant therapy for the prevention of metastases (7-11). In 1979, Bramwell and Pinedo (12) reviewed the literature of the activity of HDMTX-leucovorin in metastatic disease and found that 37 patients were treated with this regimen alone. The overall response rate was 40% (27% if patients with 25%-50% regression are excluded); the majority of responses were of brief duration. Since 1979, four more reports on the activity of HDMTX have been published. The results of Ambinder et al (13), Leber et al (14), and Pratt (15) are in sharp contrast with the results of Rosen and Nirenberg (16). The collective data of the first three authors for 17 patients are as follows: one patient had a CR lasting 3 weeks; two had PR, both lasting 7 months; and one had stable disease lasting 23 months. On the other hand, Rosen and Nirenberg observed nine CRs and 11 PRs among 30 patients, for an overall response rate of 68%.

Although toxicity associated with HDMTX is now minimal in experienced hands, the enormous financial burden of therapy, coupled with disappointing results in adjuvant studies (17), was reason to initiate this study evaluating LDMTX in patients with measurable disease. The intended trial design in which a randomization was planned between LDMTX and HDMTX had to be stopped because of low accrual. Therefore, only the LDMTX arm was continued, and among 25 patients an overall response rate of 12% (three CRs) was observed. At disease progression, 12 patients were crossed over from LDMTX to HDMTX and five of them subsequently had stable disease. Although the number of patients is small, this result weakens the hypothesis that drug resistance to MTX is relative.

In conclusion, the results obtained with LDMTX in the present study seem inferior with the pooled data of HDMTX. A randomized study comparing LDMTX with HDMTX is needed to draw definite conclusions about the dose-response relationship.

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TABLE 1.—Nonhematologic toxic effects with LDMTX*

Toxic effect	Toxicity grade— 0	1	2	3	NE†
Anorexia	22	5			
Nausea-vomiting	10	17			
Diarrhea	24	2	1		
Mucositis	19	4	2	2	
Weight loss	24	2	1		
Neurological	24	2			1
Fever	24	1	2		
Liver impairment	22	4			1
Alopecia	22	3	1		1

*Values = No. of patients.
†NE = not evaluable.

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Phase II Trials of Recombinant Leukocyte A Interferon in Disseminated Malignant Melanoma: Results in 96 Patients[1]

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Ninety-six patients with advanced malignant melanoma received thrice weekly im recombinant leukocyte A interferon (Roferon-A) in three consecutive phase II trials utilizing doses of 12 × 10^6 U/m^2, 50 × 10^6 U/m^2, and 50 × 10^6 U/m^2 plus cimetidine. The overall response rate was 22%, with median times to disease progression and survival of 3.9 and 11.3 months, respectively. For all study participants, the median times to disease progression and survival were 1.5 and 5 months, respectively. Most regressions occurred within the first month of treatment and were predominantly in soft tissue, although three patients are responding 2–3 years after onset of treatment. The most noteworthy toxic effects included a flu-type illness, anorexia, and fever (38.3–39.4°C). The median weight loss was 2.1 kg on the low-dose regimen and 5.6 kg on the high-dose program. Recombinant leukocyte A interferon in the dosages and schedule that we used has definite but limited efficacy for patients with disseminated malignant melanoma. [Cancer Treat Rep 70:619–624, 1986]

Interferons (IFNs), a class of glycoproteins produced by selected cells which have been exposed to a variety of agents (1), demonstrate a broad spectrum of immunomodulatory and antiproliferative characteristics. These include inhibition of the viral translation of messenger RNA, impairment of cellular replication (2,3), and augmented RNA toxicity on cells (4). In addition, IFNs have produced objective antitumor effects in an array of hematologic and solid tumors (5,6). IFNs have special appeal in the management of malignant melanoma. Experimental investigations, clinical trials, and the clonogenic assay confirm that these agents (5–9) can inhibit melanoma replication.

Between July 1982 and July 1984, we enrolled 97 patients into three consecutive phase II trials of recombinant leukocyte A interferon (rIFN-αA) in patients with disseminated malignant melanoma (10–12) using low-dose rIFN-μA (12 × 10^6 U/m^2), high-dose rIFN-αA (50 × 10^6 U/m^2), and high-dose rIFN-αA plus cimetidine, respectively. One patient in the cimetidine study was ineligible because of no measurable indicator lesion. The third study combined rIFN-αA with cimetidine because of the reported therapeutic enhancement of rIFN-αA by cimetidine (13). We report here an updated and pooled analysis of these studies.

MATERIALS AND METHODS

We used the same design to initially accrue 15 better-risk patients in each of these studies [Eastern Cooperative Oncology Group performance score (ECOG PS) of 0,1, and no prior chemotherapy]. If any responses were observed, an additional five better-risk patients were to be entered. The design permitted the accrual of a maximum of 15 poor-risk patients in each study (ECOG PS of 2,3, or with prior chemotherapy) concomitantly with the better-risk patients. The same eligibility criteria were employed for all three studies. To be eligible, patients had to be ambulatory (ECOG PS of 0, 1, 2, or 3) and have histologically confirmed disseminated malignant melanoma with measurable indicator lesions. In addition, patients were not eligible if they had systemic anticancer treatment or radiation therapy for at least 4 weeks prior to commencing rIFN-αA. Criteria for participation included an expected survival of at least 12 weeks; no acute illness or active viral disease; and adequate renal (serum creatinine < 1.9 mg/dl), hepatic (no elevation of direct reacting serum bilirubin), and hematologic (leukocyte count > 3000/mm^3, granulocyte count > 1000/mm^3, and platelet count > 100,000/mm^3) functions. All patients signed

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informed consent forms.

The patient characteristics of the 96 eligible patients are given in table 1. There were few meaningful differences in the distribution of the three trials (10–12), respectively, with regard to median age (56, 53, and 57 years); sex (percent of males: 74%, 50%, and 57%); no prior chemotherapy (71%, 57%, and 71%); performance status of 0,1 (84%, 90%, and 80%); and visceral dominant metastases (61%, 73%, and 66%). There were 60 males and 36 females, with a median age of 53 years. Two-thirds of patients had visceral-dominant disease and no prior chemotherapy. ECOG PSs were predominantly 0 or 1. There were 57 better-risk patients (ECOG PS of 0,1, and no prior chemotherapy) and 39 poor-risk patients (ECOG PS of 2,3, or prior chemotherapy exposure).

The rIFN-αA, supplied by Hoffmann-La Roche Inc, Nutley, NJ, was injected im into either the deltoid muscle of one arm or one of the gluteus muscles in rotation. The injected dose was 12 or 50 $\times$ 10^6 U/m^2 (10,11) three times weekly on alternate days for a planned treatment duration of 12 weeks. For patients receiving cimetidine (12), the oral dose was 300 mg four times daily. Patients were routinely premedicated on the first treatment only with oral acetaminophen and a single iv dose of hydrocortisone. Thereafter, oral acetaminophen was used for symptomatic toxicity. Patients were asked not to use aspirin or other nonsteroidal anti-inflammatory agents.

Prior to the start of treatment and before subsequent monthly assessments, each patient underwent a complete medical and neurological evaluation, measurement of indicator lesions, chest x-ray, ECG, radionuclide liver scan when clinically indicated, routine hematologic and chemical parameters, urinalysis, and serum levels of rIFN-αA and rIFN-αA antibodies. We reassessed each patient 2 weeks after the initial injection by medical history, physical examination, and hematologic and chemical parameters.

We defined objective regressions by using traditional criteria: *complete response*—the absence of all measurable disease; *partial response*—a $\geq$ 50% decrease in the product of the longest perpendicular diameters of the most clearly measurable indicator lesions without symptomatic deterioration or the appearance of new lesions; and *progressive disease*—a > 25% increase in the product of any indicator lesion or the development of new lesions. We calculated time to disease progression from the day of registration to the date of disease progression first noted.

Logistic regression was used to analyze the association of the treatment and patient characteristics with response. Time to disease progression and survival distributions were estimated by the Kaplan and Meier method (14). Log rank tests and proportional hazards modeling were used to analyze time to disease progression and death. Log hazard ratios and standard error were used to calculate confidence intervals on the hazard ratios. Prior reviews have outlined the methodology of genetic cloning and the technical aspects of recombinant IFN isolation and expression (15).

RESULTS

We observed 21 regressions among 96 patients (22%) (table 2). Fifteen patients responded within 1 month of commencing therapy. A logistic regression analysis was performed utilizing objective response as the dependent variable and independent variables, consisting of six variables describing patient characteristics [good PS (yes if ECOG PS = 0, no otherwise), prior chemotherapy (yes vs no), visceral dominant disease status (yes vs no), prior radiation therapy (yes vs no), older age (yes if $\geq$ 56 years, no otherwise), and male (yes vs no)] plus two treatment variables [high-dose IFN (yes vs no) and cimetidine treatment (yes vs no)]. The only significant covariate was visceral dominant disease status (two-sided P = 0.003) with a higher rate of response associated with nonvisceral dominant disease. Treatment variables were not significant in any model (P values for high-dose IFN and cimetidine treatment were 0.89 and 0.86, respectively, after adjustment for

TABLE 1.—Pretreatment characteristics of 96 patients treated with rIFN-αA*

Characteristic	Total	Better-risk	Poor-risk
Evaluable	96	57	39
Median age (yrs)	56	54	56
Males/females	60/36	37/20	23/16
Prior chemotherapy (yes/no)	32/64	0/57	32/7
Prior radiation therapy (yes/no)	16/80	5/52	11/28
ECOG PS (0/1/2,3)†	33/48/15	25/32/0	8/16/15
Dominant metastatic site Visceral/nonvisceral	64/32	39/18	25/14

*Unless otherwise specified, values = No. of patients.
†ECOG PS: 0 (fully active) to 4 (totally disabled).

TABLE 2.—Results of treatment with rIFN-αA and site of metastasis

Risk category	No. of responders/total patients: Visceral dominant	Nonvisceral	All patients
Better*	5†/39	10/18	15/57‡
Poor§	1/25	5/14	6/39¶

*ECOG PS of 0,1, and no prior chemotherapy.
†Indicator lesions: chest x-rays (4 patients); computerized tomographic scan of prostate for biopsy-proven disease; liver scan (not biopsied); and physical assessment of inguinal adenopathy.
‡Responses: partial, 13 patients [soft tissue, 9; lung, 3; prostate, 1 (computerized tomography-assessed)]; complete, 2 (soft tissue).
§ECOG PS of 2,3, or prior chemotherapy.
¶Responses: partial, 4 patients (soft tissue); complete, 2 (soft tissue); 1 patient had complete response of both soft tissue and liver involvement.

the effect of visceral dominant disease status).

Ninety-seven percent of study participants have experienced disease progression, and the remaining three patients have been followed for >2.1 years. The median time to disease progression for all 96 patients was 51 days (fig 1). The distributions of time to disease progression for patients in the three treatment groups were not significantly different (two-sided log rank $P = 0.37$). A Cox covariate analysis was performed using the same covariates as for the logistic analysis described above. None of the covariates were significantly associated with time to disease progression. In particular, the model containing only the two treatment variables revealed no significant association of treatment with time to disease progression (P values for high-dose IFN and cimetidine treatment were 0.42 and 0.13, respectively). The estimated times to disease progression hazard ratios (high-dose group/low-dose group, high-dose + cimetidine group/low-dose group) were 0.85 and 1.21, with a 95% confidence interval of 0.51-1.43 and 0.73-2.01, respectively. Thus, it is unlikely that there is a large time to disease progression advantage for high-dose treatment over low-dose treatment or high-dose plus cimetidine treatment over low-dose treatment.

Eighty-nine percent of all study participants have died. Follow-up on the 11 living patients ranges from 11 to 35 months. The median survival time was approximately 5 months (fig 2). The survival distributions in the three treatment groups were not significantly different (two-sided log rank $P = 0.84$). A Cox covariate analysis was performed using the same covariates as for the logistic analysis. The only covariate significantly associated with survival was ECOG PS (two-sided $P = 0.015$). That is, patients with an ECOG PS of 0 survived longer. Treatment variables were not significantly associated with survival (P values for high-dose IFN and cimetidine treatment were 0.98 and 0.74, respectively, after adjustment for the effect of good PS variable). The estimated death hazard ratios (high-dose group/low-dose group, high-dose + cimetidine group/low-dose group) were 0.99 and 1.07, with a 95% confidence interval of 0.59-1.72 and 0.63-1.83, respectively. It is unlikely that there is a large advantage to high-dose treatment over low-dose treatment or to high-dose plus cimetidine treatment over low-dose treatment with respect to survival.

Among the better-risk patients, the overall response rate was 26%. The median response duration was 4.3 months (range, 1.8-26+). Two patients have not yet progressed. A 42-year-old man with soft tissue disease remains without evidence of disease 25 months after

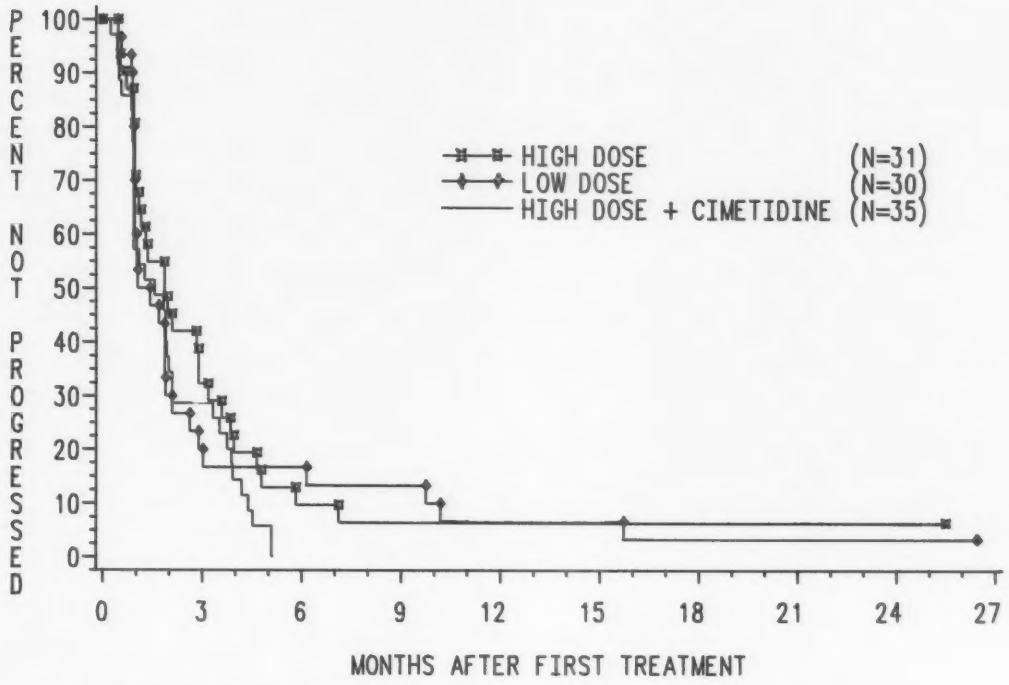

FIGURE 1.—Time to disease progression after start of rIFN-αA.

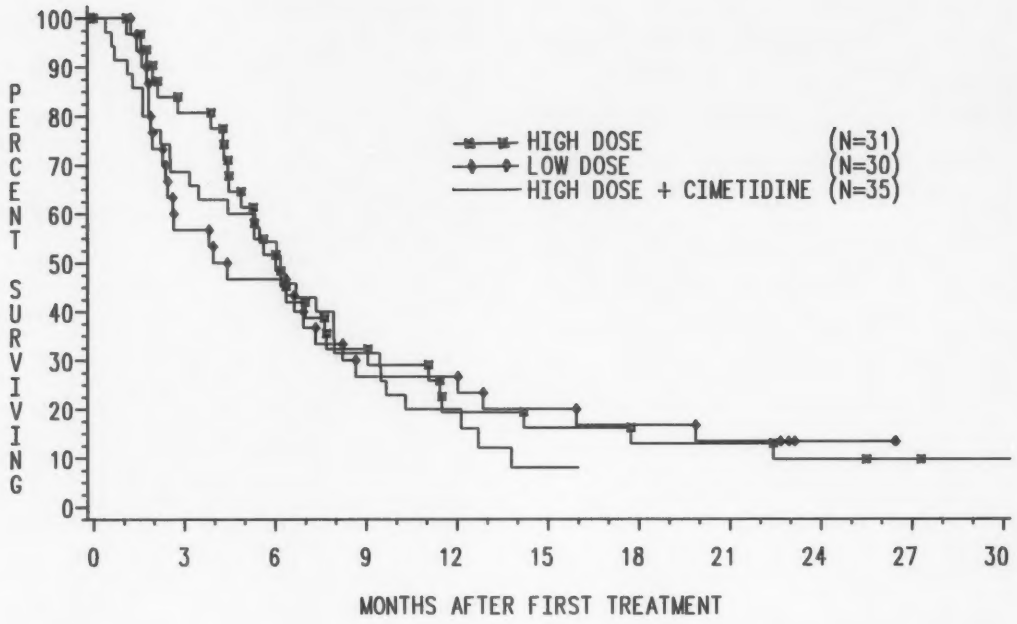

FIGURE 2.—Survival after start of rIFN-αA.

the onset of therapy. A 55-year-old woman with pulmonary and soft tissue disease continues to have a partial response for 26 months.

Among the poor-risk patients, the response rate was 15%, with a median response duration of 4.1 months (range, 2.1-34.8+). Of particular note is a 56-year-old woman with easily measurable, biopsy-proven soft tissue disease and a liver scan consistent with metastatic disease but without tissue confirmation. She remains without evidence of disease 34.8 months following the commencement of IFN. A 45-year-old woman demonstrated a partial response of extensive subcutaneous disease for 15 months.

Characteristics of the three patients currently without disease progression are listed in table 3.

Toxic Effects

Among the 31 patients who received 50 × 10^6 U/m^2 three times weekly, most experienced moderate-to-severe chills, fatigue, and fever (38.3-39.4°C). Among all 96 patients, approximately 50% required dosage reductions due to complications. Among the 13 patients who remained on study for 12 weeks, only six could tolerate the full dose regimen. Anorexia affected 58% of patients and was concomitant with a median maximum weight loss of 5.6 kg (range, 0.9-23.6). An acute confusional state temporally related to therapy occurred in 23% of patients (table 4).

Among the 30 patients who received 12 × 10^6 U/m^2 three times weekly, we observed similar sequelae of

TABLE 3.—Characteristics of long-term responding patients

Patient No.	Age (yrs)/sex	Prior therapy	Indicator lesion	Dimensions of measurable disease (cm)	Response	Duration (mos)	Interval from last rIFN-αA (mos)
1	42/M	None	Soft tissue	0.5 × 0.5-0.8 × 0.8	Complete	25	21
2	56/F	Chemo/Rx*	Soft tissue Liver scan without tissue confirmation	4 × 3; 2 × 2	Complete Complete	34.8	32
3	55/F	None	Soft tissue Chest x-ray	1.8 × 1.8; 0.9 × 1.9 2 × 2	Complete Partial	26	23.4

*Chemo = chemotherapy; Rx = radiation therapy.

TABLE 4.—Clinical toxic effects of rIFN-αA 3 times weekly*

Toxic effect	50×10^6 U/m^2 (N = 31)	12×10^6 U/m^2 (N = 30)	50×10^6 U/m^2 + cimetidine (N = 35)
Moderate to severe—			
Fever (> 38.9°C)	100	80	89 (N = 28)
Fatigue	87	50	77
Anorexia	58	47	63
Myalgias	19	27	49
Nausea	16	33	34
Vomiting	13	13	17
Confusion	23	3	11
Maximum weight loss (kg)			
Median	5.6 (N = 28)	2.1 (N = 29)	3.6 (N = 30)
Range	0.9-23.6	0-8.4	0-19.5

*Unless otherwise specified, values = % of patients.

fever and anorexia. However, moderate-to-severe fatigue was less frequent (50% vs 87%) and the median maximum weight loss was only 2.1 kg (range, 0-8.4). Confusion was observed in only 3% of patients.

Among the 35 patients who received 50×10^6 U/m^2 three times weekly with cimetidine, fever (> 38.3°C), fatigue, and anorexia were quite similar to our initial high-dose study. However, confusion was less frequent (11%). The median weight loss, 3.65 kg (range, 0-19.5), was intermediate between the two prior studies.

Hematologic and hepatic toxic effects were generally reversible, transient, and of no apparent clinical significance (table 5).

DISCUSSION

In these three consecutive phase II trials involving 96 patients, we have documented some objective regressions among a proportion of patients with disseminated malignant melanoma. Most of the responses were relatively transient and were confined predominantly to soft tissue metastases. However, regressions did occur in some visceral sites. The overall median time to progression of 1-2 months and the median survival of 4-6 months were remarkably consistent among the three trials. These durations are generally similar to the results achieved by systemic chemotherapy for patients with disseminated malignant melanoma.

We did not design our studies within the context of a prospective, randomized trial which would allow for confident comparison of dose-response relationships from rIFN-αA in advanced malignant melanoma. Nevertheless, we could not document any obvious benefit from the high-dose regimen. Two recent trials addressing this issue, albeit in renal cell carcinoma (RCC), are noteworthy. A randomized comparison in RCC assessed high doses of human leukocyte α-IFN [1×10^6 vs 10×10^6 U/day $\times$ 28 days (16)]. Six of seven regressions occurred from the high-dose program, and three were major responses. Another randomized trial in RCC utilized the same recombinant-derived preparation which we employed (17). The first 30 patients received daily doses of either 2×10^6 or 20×10^6 U/m^2. There were no objective regressions from the low-dose program, but a 27% response rate was achieved from the higher dose. An additional 26 patients who were not randomized confirmed the higher response rate. Although optimum dosages of rIFN-αA are not yet established, it appears for RCC and possibly malignant melanoma that a therapeutic plateau is achieved at doses of $12\text{-}20 \times 10^6$ U/m^2, and there may be little advantage from exceeding this dose of rIFN-αA.

Our observations and those of other investigators (5,6,18) clearly indicate that IFNs as currently used in single-agent therapy for malignant melanoma have not meaningfully altered the presently inexorable course of disseminated disease. It also appears that current studies addressing phase II trials of IFNs may have been somewhat optimistic in estimating the objective response rates among patients with malignant mela-

TABLE 5.—Hematologic and hepatic toxic effects of rIFN-αA 3 times weekly

Toxic effect	50×10^6 U/m^2	12×10^6 U/m^2	50×10^6 U/m^2 + cimetidine
Median nadir leukocyte count (range)*	3.1 (1.6-7.3)	3.9 (1.9-8.8)	3.1 (1.3-8.4)
Median nadir platelet count (range)*	158 (56-296)	186 (76-472)	197 (100-385)
SGOT > normal range (12-31 μg/L)	86%	97%	97%

*Values = cells $\times 10^3$/mm^3.

noma (19). Nevertheless, we were encouraged by durable and clinically meaningful regressions in selected individuals.

Although IFNs have limited efficacy in traditional phase II trials, these agents have enormous therapeutic appeal to complement cytotoxic regimens. The antitumor activity, relative absence of substantial gastrointestinal and hematologic toxicity,. and possible synergism from animal tumor models make IFN conceptually attractive in combination with chemotherapeutic approaches (20-23). Japanese investigators (24) have also confirmed synergistic interactions between human lymphoblastoid IFN and diverse cytotoxic agents including prednisolone.

Concomitant immunoregulatory regimens with IFNs are of keen interest. An intriguing area of profound theoretical promise is the combination of IFNs with tumor necrosis factor, another type of cytotoxic glycoprotein (25-27). The role of nonsteroidal anti-inflammatory agents to ameliorate toxic effects from IFN also needs to be addressed, since these agents may not inhibit the antiproliferative activity of IFN (28).

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Effect of Hyperthermia on the In Vitro Metabolism of Doxorubicin[1,2,3]

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The effect of hyperthermia on the uptake and metabolism of doxorubicin (ADM) was studied in in vitro systems. ADM uptake in rat liver slices was not affected by increasing the temperature from 37°C to 43°C. In rat liver homogenates, the aerobic transformation of ADM was low and was not affected by hyperthermia. Approximately 90% of the parent drug remained unchanged after 60 minutes of incubation, and two metabolites, adriamycinol and a polar metabolite, were formed in small amounts. Under anaerobic conditions, ADM was quickly and extensively converted to two metabolites identified as 7-deoxyadriamycinol aglycone and 7-deoxyadriamycin aglycone. Whereas the disappearance of ADM and the formation of 7-deoxyadriamycin aglycone were not modified by the hyperthermic conditions, there was a slight but significant increase of the formation of 7-deoxyadriamycinol alycone (area under the concentration versus time curve in μM × minute: 216 ± 24 at 37°C; 235 ± 24 at 39.5°C; and 271 ± 8 at 42°C; $P \leq 0.05$). However, the percentage of dA3 was not significantly different at the end of the incubation. [Cancer Treat Rep 70:625–629, 1986]

Present anticancer strategy involves trials of new agents, new combinations of chemotherapeutic agents, and combined-modality therapy using chemotherapy, radiotherapy, and surgery. Hyperthermia (HT) is a totally different modality to add to existing treatments. In vitro and in vivo studies have shown that tumor cells are killed by heat (1,2) and have greater thermal sensitivity than normal cells (3). Several trials are now conducted in man to define the therapeutic value of HT with or without antineoplastic agents (4–7).

Little is known about the effect of HT on the pharmacologic behavior of the antineoplastic drugs. Doxorubicin (ADM) is one of the major antitumor agents and its pharmacology has been well-described in euthermic patients (8–10). In addition, ADM was quickly considered as a candidate for combination with HT; a synergism between the two treatment modalities was demonstrated in mammalian cells by Hahn et al (11). Therefore, it was important to investigate the effect of HT on the pharmacology of ADM.

Clinical information regarding the effect of HT on the metabolism of ADM has been obtained from a trial of whole-body HT plus ADM and cyclophosphamide (12). HT did not affect the plasma profile of ADM, but there was a significant increase of the area under the plasma concentration versus time curve for ADM-derived aglycones after hyperthermic treatment. The interaction between HT and the metabolism of ADM has also been investigated in animal models. In a study with rabbits, Mimnaugh et al (13) have shown that the clearance rate of ADM from the plasma was similar in normothermic and hyperthermic (42.3°C) animals. Using perfused isolated rat liver as a model, Skibba et al (14) observed a decrease of bile flow and of the excretion of ADM and total ADM equivalents in hyperthermic conditions. The area under the concentration versus time curve in perfused plasma was unchanged for parent drug, but increased by 100% for total drug equivalents. One problem common to these two animal studies is that plasma and biliary levels are the endpoint of physiologic homeostasis and several processes: uptake of the drug by liver cells, metabolism, and secretion into bile or plasma.

In this study, we have tried to dissociate these sequential steps by studying separately the uptake and metabolism of ADM by rat liver in vitro.

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MATERIALS AND METHODS

Reagents

β-Nicotinamide dinucleotide phosphate (NADP), glucose-6-phosphate, and glucose-6-phosphate dehydrogenase were obtained from Sigma Chemical Co (St. Louis, MO). ADM was purchased from Farmitalia (Milan, Italy) and further purified by chromatography on a silicic acid column (15). All other reagents were reagent grade.

Animal and Tissue Preparation

Male Sprague-Dawley rats (250-350 g), obtained from Charles River Breeding Laboratories, Inc (Wilmington, MA), were used in all experiments. The animals were fed a standard chow diet (National Institutes of Health Rat and Mouse Ration, Ralston-Purina, St. Louis, MO) and water ad libitum; the rats were housed three to five per cage and maintained in a controlled environment with light and dark cycles of 12 hours each.

All animals were killed between 8 and 9 AM. They were stunned by a blow to the head, decapitated, exsanguinated, and quickly hepatectomized, after which the excised livers were placed in iced 1.15% KCl solution. All further procedures for the preparation of the homogenates were carried out at 0°C-4°C. A 25% whole homogenate fraction was prepared in 1.15% KCl solution with a glass homogenizer and a Teflon pestle (15 strokes). The homogenate was centrifuged at 9000 × *g* for 20 minutes; the supernatant was used for the various incubations.

Liver slices (0.5 mm) were prepared with a Stadie Riggs microtome (Arthur H. Thomas Co, Philadelphia, PA).

Study of the Metabolism of ADM by Rat Liver Homogenates

The standard incubation reaction mixture contained the following constituents: NADP (0.5 mM), glucose-6-phosphate dehydrogenase (0.5 U/ml), magnesium chloride (1.54 mM), and the volume of 9000 × *g* supernatant obtained from 0.125 or 3 g of wet liver for the anaerobic and aerobic incubations, respectively. The total volume was adjusted to 25 ml with Hanks' balanced salt solution (HBSS). All reactions were started by the addition of ADM. The mixture was incubated at 37°C, 39.5°C, or 42°C in a Dubnoff metabolic shaker (120 oscillations/minute) under continuous flow of either oxygen or nitrogen. At appropriate times, duplicate 0.5-ml samples were removed and extracted with 2 ml of chloroform-isopropanol (vol:vol; 1:1) and assayed for ADM and its metabolites as described below.

Study of ADM Uptake by Liver Slices

Four to six liver slices weighing a total of 300-400 mg/test were incubated in the presence of ADM (5-10 μM) in a total volume of 3 ml of HBSS at 37°C, 39°C, 41°C, or 43°C. Studies were initiated by the addition of ADM. The incubations were carried out in a Dubnoff metabolic shaker (120 oscillations/minute) under room air.

After incubation, an excess of HBSS was added to the incubation mixture and the slices were separated by centrifugation for 2 minutes at 2500 × *g*. This procedure was repeated twice. After the third centrifugation, the slices were homogenized in 2 ml of chloroform-isopropanol (vol:vol; 1:1) with a glass homogenizer fitted with a Teflon pestle. ADM and its metabolites were assayed as described below.

Assay of ADM and Its Metabolites

After extraction with chloroform-isopropanol (vol:vol; 1:1), the mixture was saturated with ammonium sulfate and centrifuged at 27,000 × *g* for 10 minutes. The organic phase was collected and an aliquot of 0.5 ml from each duplicate sample was added to 1.5 ml of isopropanol-2.16 N sulfuric acid (vol:vol; 75:25) and assayed for total fluorescence content. The remainder of the organic phase from the duplicate samples was pooled, concentrated to dryness under nitrogen, and redissolved in 100 μl of chloroform-methanol-acetic acid-water (vol:vol:vol:vol; 80:20:14:6). Fluorescent areas were identified with a 254-nm UV lamp, scraped, and eluted with isopropanol-2.16 N sulfuric acid (vol:vol; 75:25). Corresponding areas of the silica gel containing no sample were used as blanks for the fluorescence assay. All fluorescence determinations were performed on an Aminco-Bowman Spectrofluorimeter (SLM Instruments, Inc, Urbana, IL) at an exitation wavelength of 470 nm and an emission wavelength of 585 nm. The percentage of each fluorescent species was expressed from its relative concentration on the chromatogram after correction for nonspecific fluorescence present in an ADM-free incubation medium.

Mass Spectral Analyses

Mass spectral analyses were done on a VG Micromass 30F mass spectrometer (VG Analytical, Altrincham, England) operated under VG data systems 2040 computer control. Spectra were obtained every 7 seconds over a range from 600 to 20 atomic mass units at a scan rate of 10 seconds/decade. Source conditions were 200°C, 70-electronvolt ionizing voltage, 170-μAmp trap current, and 4-kV accelerating voltage.

Statistical Tests

A Student's paired t test was used for all of the statistical comparisons.

Uptake of ADM by Rat Liver Slices

The uptake of ADM by liver slices appeared to be a quick and saturable process (fig 1). At 37°C, the amount of ADM recovered from the slices increased from 3.8 ± 3.1 pmols/mg of liver at 0 minute to 44.9 ± 2.3 pmols/mg of liver at 30 minutes and remained stable thereafter up to 90 minutes. The uptake of ADM was not affected by the hyperthermic conditions (39°C, 41°C, or 43°C). There are no statistical differences in the uptake of ADM at the four temperatures at any time.

ADM was the major anthracycline extracted at any time. Other species present in the preparation reflected the metabolism of ADM, which was found to be minimal under aerobic conditions (*see* below). Three different metabolites were identified, including adriamycinol, a polar metabolite, and an aglycone, but the total of these metabolites generally accounted for < 10% of the total fluorescence. Therefore, no difference was found in the uptake of the total equivalent of anthracyclines at the four different temperatures.

Metabolism of ADM Under Aerobic Conditions

Under aerobic conditions, ADM was slowly metabolized to two metabolites; they were identified as adriamycinol and a polar conjugate according to their chromatographic mobility on the silica gel chromatography. HT did not appear to significantly affect the aerobic metabolism of ADM. The metabolism of ADM was limited and no statistical differences are evident among the three temperatures (table 1).

Metabolism of ADM Under Anaerobic Conditions

Under anaerobic conditions, ADM was quickly metabolized and transformed into two different aglycones, identified as 7-deoxyadriamycinol aglycone (dA3) and 7-deoxyadriamycin aglycone (dA4) (fig 2) according to their chromatographic mobility on the silica gel chromatography. In addition, their structure was confirmed by mass spectroscopy. At 37°C, approximately 85% of ADM was converted to dA4. Subsequently, the amount of dA4 decreased while dA3 progressively increased (fig 3).

The effect of HT on the anaerobic metabolism of ADM is shown in figure 3. The following parameters were not affected: percentage of dA4 at 5 and 60 minutes and area under the curve for ADM and dA4. A slight increase of the formation of dA3 was noted. The rates of initial formation of dA3, calculated from the initial linear portion of the curve of the percentage of dA3 versus time, were 0.18 ± 0.6 μM/minute at 37°C, 0.19 ± 0.02 μM/minute at 39.5°C, and 0.21 ± 0.05 μM/minute at 42°C. These differences, however, are not significant ($P = 0.60$). Similarly, the percentage of dA3 formed at 60 minutes increased from 86% ± 4% at 37°C to 88% ± 2% at 39.5°C and to 90% ± 1% at 42°C ($P = 0.20$). The area under the concentration versus time curve for dA3 was significantly increased; the areas under the concentration versus time curve for this metabolite were 216 ± 24 μM × minute at 37°C, 235 ± 24 μM × minute at 39.5°C, and 271 ± 8 μM × minute at 42°C. The difference between 37°C and 42°C is statistically significant ($P \leq 0.05$), whereas it is not between 37°C and 39.5°C and between 39.5°C and 42°C.

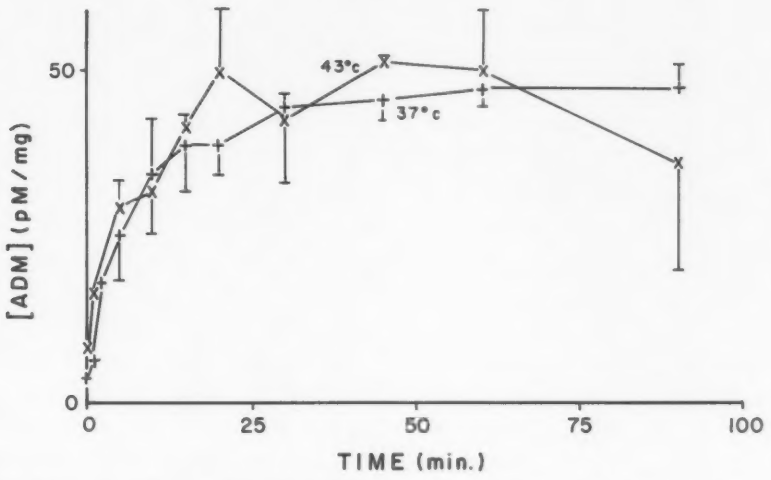


FIGURE 1.—Uptake of ADM by rat liver slices. ADM (5 μM) was incubated in the presence of 300–400-mg liver slices at 37°C (+ ——— +) or 43°C (× ——— ×) (the curves at 39°C and 41°C have been omitted from the fig for clarity). Each point represents the mean of 3 experiments. Bars represent SDs.

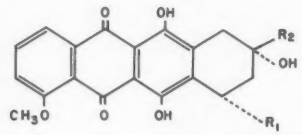
TABLE 1.—Effect of HT on the aerobic metabolism of ADM

	Mean ± SD at—*			P value
	37°C	39°C	42°C	
ADM at 60 mins (%)	94.5 ± 4.1	89.9 ± 2.3	86.2 ± 5.9	0.30
Adriamycinol at 60 mins (%)	3.6 ± 4.0	7.9 ± 1.4	7.4 ± 3.7	0.20
Polar metabolite at 60 mins (%)	1.4 ± 0.5	2.2 ± 1.6	3.9 ± 1.2	0.20
Area under the curve (μM × min)				
ADM	256.5 ± 33.7	264.2 ± 39.4	281.3 ± 20.0	0.50
Adriamycinol	9.3 ± 11.2	22.7 ± 2.9	18.0 ± 13.3	0.40
Polar metabolite	4.1 ± 1.6	6.3 ± 3.0	8.0 ± 3.4	0.30

* ADM (5 μM) was incubated under aerobic conditions for 60 mins at the indicated temperatures in the presence of rat liver homogenate. Samples were obtained at specified times and ADM and metabolites were assayed by thin-layer chromatography.

DISCUSSION

HT is a new anticancer strategy under clinical investigation. Several trials are now being conducted to define the therapeutic value of HT alone or with various anticancer drugs (4-7). ADM was promptly considered as a candidate for combination with HT, since a synergism between the two treatment modalities was demonstrated in mammalian cells by Hahn et al (11). In a clinical trial with a combination of cyclophosphamide and ADM with or without HT conducted at the University of Maryland Cancer Center in soft tissue sarcomas (12), an increase of the area under the plasma concentration versus time curve for the aglycones of ADM was observed after hyperthermic treatment. However, these results are complicated by the interference of cyclophosphamide. The metabolism of cyclophosphamide is affected by HT (16,17), and cyclophosphamide interacts with the cytochrome P450 reductase (18), a key enzyme in the conversion of ADM to aglycones (19). Animal studies on HT and ADM (13,14) show conflicting results. In the present study, we have used an in vitro model to separate the uptake and metabolism of ADM by rat liver. The first step of the hepatic disposition of ADM is the uptake of the drug by the hepatocytes. In this study, we did not find any effect of HT on the uptake of ADM by rat liver slices.



COMPOUND	R_1	R_2
ADRIAMYCIN (ADM)	DAUNOSAMINE	$C(=O)-CH_2OH$
7-DEOXYADRIAMYCIN AGLYCONE (dA4)	H	$C(=O)-CH_2OH$
7-DEOXYADRIAMYCINOL AGLYCONE (dA3)	H	$CH(OH)-CH_2OH$

FIGURE 2.—Structure of ADM, dA3, and dA4.

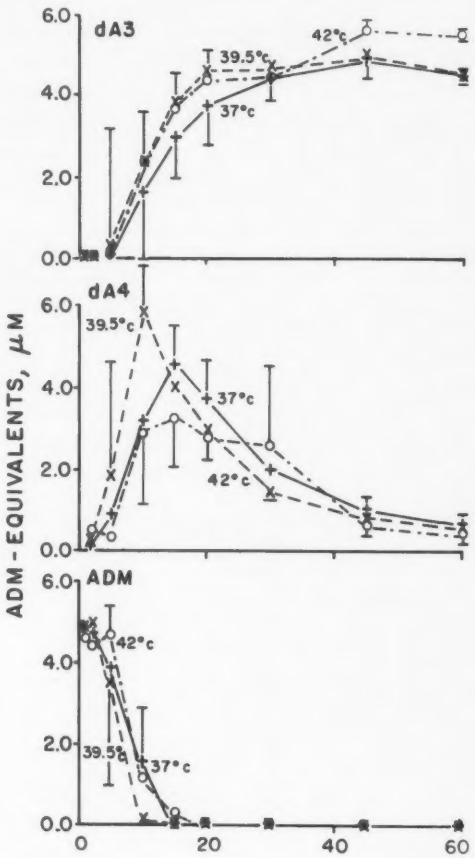


FIGURE 3.—Effect of HT on the anaerobic metabolism of ADM. ADM (5 μM) was incubated in the presence of rat liver homogenate under nitrogen at 37°C, 39.5°C, or 42°C. Each point represents the mean of 3 experiments. Bars represent SDs. *Lower panel*—disappearance of ADM; *middle panel*—formation of dA4; and *upper panel*—formation of dA3.

This is in contrast to the findings by Hahn et al (11), who showed an increased uptake of ADM by Chinese hamster cells. This might reflect an intrinsic difference between these cells and hepatocytes, but could also be related to the conditions in which the tests were performed, since we used rat liver slices while isolated exponentially growing cells were investigated by Hahn.

Under aerobic conditions, the liver tissue carried out limited biotransformation of ADM and no effect of HT was detected. This is in agreement with the fact that ADM is a good substrate for the NADPH-cytochrome P450 reductase; this enzyme converts ADM to semiquinone free radicals, which are converted back to ADM in the presence of oxygen (19). Since these semiquinone free radicals are intermediates in the formation of aglycones, very low levels of aglycones are expected to be seen under aerobic conditions. This is consistent with our observations.

On the contrary, under anaerobic conditions, the semiquinone free radicals undergo rearrangement and spontaneous cleavage of the glycosidic fraction to produce 7-deoxyaglycones. 7-Deoxyaglycones are excreted by man in urine and bile, indicating that the glycosidic cleavage of anthracycline antibiotics does occur under physiological conditions in man, probably in subcellular anaerobic areas (15,19). Two aglycones were observed in our experimental system, ie, dA3 and dA4. HT appeared to stimulate slightly the formation of dA3; this effect may be related to an enhanced activity of the enzyme reducing dA4 into dA3 at higher temperatures. However, no significant difference could be detected at the end of the incubation and no effect at all was observed on the formation of dA4 and the disappearance of ADM. Thus, the effect of HT on the metabolism of ADM also appeared to be minimal under anaerobic conditions.

In conclusion, this in vitro study fails to show any significant effect of HT on the disposition of ADM by rat liver in vitro. The results are in complete agreement with those obtained by Mimnaugh et al (13) with the rabbit model. In a different model using perfused isolated rat liver, Skibba et al (14) observed a decrease of bile flow and of the excretion of ADM and total ADM equivalents, as well as an increase of the area under the curve in perfused plasma for total ADM equivalents. Such a result was seen after a 3-hour exposure to heat. Considering our results and those obtained by Skibba et al (14) and Mimnaugh et al (13), it seems that HT affects primarily the bile flow without modifying the uptake and metabolism of the drug by hepatocytes. When the bile flow is reduced for a sufficient period of time, as in Skibba's study, the elimination of ADM and its metabolites is reduced, with a concomitant increase of the area under the plasma concentration versus time curve.

In man, an increased area under the curve was observed for the aglycones after hyperthermic treatment (12). Since ADM was combined with cyclophosphamide, this phenomenon could be related to the effect of HT on the disposition of ADM, an effect of HT on the interaction between the two drugs, or both. The available data suggest that HT can indeed modify the disposition of ADM through an effect on bile flow. The effect of HT on the interaction between ADM and cyclophosphamide remains to be investigated.

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Flavone Acetic Acid: A Novel Agent With Preclinical Antitumor Activity Against Colon Adenocarcinoma 38 in Mice[1,2]

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Flavone acetic acid, given on Days 2 and 9 at a dose of 267 mg/kg, inhibited tumor growth completely in 60%–80% of mice with early-stage Colon Adenocarcinoma 38. The therapeutic efficacy of the flavone against this tumor was retained when the sites of tumor implantation and drug administration were separated. Flavone acetic acid also caused regression of advanced (500-mg) Colon 38 tumors, with greatest efficacy observed following administration of high individual dose rather than high total dose. Unlike many previous potential anticancer agents, only modest activity was observed for this compound against either P388 or L1210 leukemia. [Cancer Treat Rep 70:631–635, 1986]

Early in the drug development program of the National Cancer Institute (NCI) (Bethesda, MD), > 200 flavones were evaluated for antitumor activity in the in vivo antitumor screens in use at that time. None of the compounds demonstrated antitumor activity in the early screens which included Adenocarcinoma 755, Sarcoma 180, and L1210 leukemia. However, in 1971 quercetin, the first flavone ever acquired, was retested and discovered to moderately inhibit the growth of ip implanted P388 leukemia, increasing the life span of the tumor-bearing mice by 27%–32% (NCI, unpublished data). At that time, the level of P388 activity demonstrated by quercetin was not considered sufficient to warrant further investigation. However, with the initiation of a new screening experiment in 1975 utilizing P388 leukemia as a prescreen and a new panel of solid tumors for secondary evaluation (1), we reexamined selected types of compounds. The availability of a series of flavones from Lyonnaise Industrielle Pharmaceutiques (LIPHA) and our desire to utilize the new tumor panel to discover potential antitumor agents with activity against solid tumors prompted us to screen selected flavones in the new system.

The flavone acetic acid ester (fig 1) emerged as a lead, demonstrating good activity against sc implanted murine Colon Adenocarcinoma 38 following ip administration. Since this system had proven to be very refractory to most anticancer drugs (2), the flavone acetic acid ester was selected for development to clinical trials by the NCI. However, it was later discovered that, when the ester was administered iv rather than ip, doses which had been optimally effective ip were acutely lethal iv (table 1). While a 267-mg/kg dose inhibited tumor growth completely in 80% of the mice when administered ip on Days 2 and 9, a 50-mg/kg dose given iv on the same treatment days caused 80% of the mice to die, 40% within 24 hours of each injection. Lower iv doses demonstrated no significant therapeutic efficacy. On the suspicion that the undesirable iv effects might be related to the local anesthetic, spasmolytic, nicotinolytic, and tranquilizing properties sometimes observed with basic esters of carboxylic acids (3), flavone acetic acid (fig 1) was tested against the Colon 38 tumor. We report the results of these studies and discuss the anticancer potential of flavone acetic acid, which is scheduled to start phase I clinical trials in late 1985.

METHODS

Flavone acetic acid was synthesized by LIPHA (4) and acquired through the NCI Liaison Office, Brussels.

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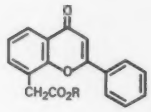

NSC	R
347512	H
293015	$CH_2\ CH_2\ N(C_2H_5)_2 \cdot HCl$

FIGURE 1.—Structures of flavone acetic acid and its ester.

Antitumor testing was conducted through the screening program of the Drug Evaluation Branch, Developmental Therapeutics Program (DTP), Division of Cancer Treatment (DCT), NCI, according to published protocols (5,6). Mice and tumor lines were obtained through the Animal Genetics and Production Branch, DTP, DCT, NCI. For the Colon 38 studies using early-stage tumor, $B6C3F_1$ (table 1) or $B6D2F_1$ (tables 2 and 3) mice were implanted sc with 60–80-mg tumor fragments on Day 0 and treatment was initiated 48 hours later. In each experiment, 39 or 40 tumored control mice received vehicle injections and groups of ten tumored mice received each dose of flavone acetic acid ester or flavone acetic acid to be evaluated. In the schedule-dependency study, parallel groups of eight normal (nontumored) mice also received identical drug injections as the tumored mice. Anticancer activity was assessed on the basis of percent tumor inhibition calculated from median tumor weights on Day 20. Tumor weights were derived from caliper measurements of the tumors using the formula for a prolate ellipsoid: Tumor weight (mg) = $(l \times w^2)/2$, where l and w are the tumor length and width (mm), respectively. The percent tumor inhibition was calculated as 100 minus [(median tumor weight of treated mice/median tumor weight of control mice) × 100%]. Mice with nonpalpable tumors were considered to be tumor-free.

For Colon 38 studies using an advanced tumor, $B6D2F_1$ mice were implanted sc with 60–80-mg fragments on Day 0 and treatment was initiated when tumors had grown to approximately 500 mg (Day 14 for experiment in table 4). On Day 14, the control median tumor weight was 488 mg and the median tumor weights of the treatment groups ranged from 384 to 588 mg. Evaluation of anticancer activity was based on tumor-free survivors and treated minus control (T–C) values (tumor growth delay), where T and C are the median times (days) for the treated and control tumors, respectively, to reach a predetermined size (1500 mg for the studies reported here). Tumor-free survivors and mice dying from drug toxicity were excluded from the T–C calculations. A treated tumor-bearing mouse was presumed to have died of drug toxicity if its day of death was significantly less ($P < 0.05$) than the corresponding day of death in the untreated control group; if it died with a tumor ⩽ 600 mg prior to 45 days after last day of treatment; or if it had regressing tumor prior to 15 days after the last day of treatment.

RESULTS

The activity of flavone acetic acid against the sc implanted Colon Adenocarcinoma 38 following both ip and iv treatment is shown in table 2. With both routes of administration, a dose of 356 mg/kg given on Days 2 and 9 caused a number of drug-related deaths (deaths occurred during treatment or within 24 hours of last treatment), while a 267-mg/kg dose inhibited tumor growth completely in 60%–80% of the mice.

Additional studies using the early-stage Colon 38 suggested that the antitumor activity of flavone acetic acid in mice correlated more with the size of the individual dose than with total dosage (table 3). Evaluation of the tumors on Day 20 showed that a single ip treatment with 200 mg/kg on Day 2 inhibited tumor growth completely in nine of ten mice. A similar response (seven of ten animals without tumor) was obtained following two 150-mg/kg treatments given 6 hours apart, but two 200-mg/kg injections were not tolerated by the

TABLE 1.—Activity of flavone acetic acid ester against sc Colon Adenocarcinoma 38: comparison of ip and iv treatment

Ip treatment on Days 2 and 9				Iv treatment on Days 2 and 9			
		No. of —				No. of —	
Dose (mg/kg/injection)*	% tumor inhibition on Day 20†	Tumor-free mice on Day 20	Survivors/ total No. on Day 20‡	Dose (mg/kg/injection)*	% tumor inhibition on Day 20†	Tumor-free mice on Day 20	Survivors/ total No. on Day 20‡
356	Toxic§	6	6/10	50	Toxic§	0	2/10
267	100	8	8/10	37.5	37	0	8/10
200	96	4	10/10	28.1	31	2	10/10
150	90	0	10/10	21.1	14	0	10/10
112.5	46	0	10/10	15.8	-9	0	9/10

*Bolus injections of drug in saline.
†Median weight of control tumors was 1100 mg.
‡All 40 control animals were alive on Day 20.
§< 65% of mice alive on Day 20 (6).

TABLE 2.—Activity of flavone acetic acid against sc Colon Adenocarcinoma 38: comparison of ip and iv treatment

Dose (mg/kg/injection)*	Ip treatment, Days 2 and 9			Iv treatment, Days 2 and 9		
	% tumor inhibition on Day 20†	No. of —		% tumor inhibition on Day 20†	No. of —	
		Tumor-free mice on Day 20	Survivors/ total No. on Day 20‡		Tumor-free mice on Day 20	Survivors/ total No. on Day 20‡
356	100	7	7/10	Toxic§	2	2/10
267	100	6	10/10	100	8	9/10
200	58	2	10/10	100	7	9/10
150	33	0	10/10	85	2	10/10
112	10	0	9/10	0	1	10/10

*Bolus injections of drug in 5% sodium bicarbonate.
†Median weight of control tumors was 1968 mg.
‡Of 40 control mice, 2 died on Day 20.
§< 65% of mice alive on Day 20 (6).

tumor-bearing mice; nine of ten mice receiving the latter doses died within 48 hours (data not shown). The number of tumors responding to treatment decreased when the number of injections on Day 2 was increased to four and the interval between each injection was decreased to 3 hours. The highest nontoxic dose on this schedule was 84 mg/kg/injection (total dose, 336) and caused complete inhibition of tumor growth in only three of ten mice. With a single drug injection per day, two courses of treatment given 7 days apart gave similar therapeutic results at the same individual dosage level as a single course. While ten of ten and six of ten mice receiving 200- and 150-mg/kg doses, respectively, on Days 2 and 9 had no tumor on Day 20, nine of ten and four of ten mice were without tumor following treatment with the same doses on Day 2 only. To determine whether treatment had merely delayed tumor appearance and growth, treated mice were held until Day 60. The majority of the mice free of tumor on Day 20 had no tumor on Day 60.

With the early-stage Colon 38 tumor, the marked tumor growth inhibition on most of the treatment schedules precluded comparison of regimen effectiveness. Thus, the effect of schedule on the antitumor activity of flavone acetic acid in mice was explored further using an advanced-stage tumor (table 4). A 160-mg/kg dose given once on staging day (Day 14) produced six of ten tumor-free survivors on Day 100 and a 20.7-day tumor regrowth delay in the four mice with tumor. Although the 200-mg/kg dose resulted in seven of ten tumor-free survivors, it was lethal to 20% of the mice, and the 128-mg/kg dose resulted in one of ten tumor-free survivors and a tumor regrowth delay of 9.1 days. A second dose of 160 mg/kg administered 7 or 14 days after the first (every 7 days × 2 or every 14 days × 2) did not significantly increase the therapeutic effects of flavone acetic acid. The optimal single dose (160 mg/kg/injection) could not be administered twice within 6 hours (every 6 hours × 2) due to increased lethality, but a lower dose (128 mg/kg/injection) demonstrated similar efficacy. Optimal doses on the long-term schedules (daily × 5 and daily × 9) resulted in the least number of tumor-free survivors and minor tumor regrowth delays. Although the total doses that could be administered were higher on the long-term schedules, individual doses were lower.

TABLE 3.—Activity of flavone acetic acid against sc Colon Adenocarcinoma 38: influence of treatment schedule

Ip treatment schedule	Dose range evaluated (mg/kg/injection)*	Optimal dose (mg/kg/injection)	Total optimal dose (mg/kg)	No. of —		
				Tumor-free mice/ total No. on		Nontumored control survivors/ total No. on Day 60
				Day 20	Day 60	
No treatment†				0/39		
Day 2 only	356-112	200	200	9/10	8/10	7/8
Every 6 hrs × 2, Day 2 only	267-84	150	300	7/10‡	6/10‡	8/8
Every 3 hrs × 4, Day 2 only	200-47.3	84	336	3/10	1/10	7/8
Every 7 days, Days 2 and 9	356-112	200	400	10/10	10/10	7/8

*Experimental formulation used: freeze-dried powder containing 250 mg of flavone acetic acid and sufficient sodium hydroxide to adjust pH to 7-9 when reconstituted with 5 ml of sterile water; further dilution was made with saline.
†Median weight of control tumors was 1795 mg.
‡One drug death within 24 hrs of last treatment.

TABLE 4.—Activity of flavone acetic acid against the established Colon Adenocarcinoma 38

Ip treatment schedule	Dose range evaluated (mg/kg/injection)*	Dose (mg/kg/injection)	Total dose (mg/kg)	Days to reach 1500 mg	T-C values (days)†	Tumor-free survivors on Day 100	Drug deaths/total	
							Tumor-implanted mice	Nontumored controls by Day 60
No treatment				17.9		0/40		
Every 6 hrs × 2, Day 14	200-81.9	160	320	42.4	24.5	2/10	5/10	3/8
		128‡	256	52.3	34.4	5/10	2/10	0/8
		102.4	204.8	18.5	0.6	2/10	1/10	0/8
Every day × 1, Day 14	250-102.4	200	200	18.6	0.7	7/10	2/10	0/8
		160‡	160	38.6	20.7	6/10	0/10	0/8
		128	128	27.0	9.1	1/10	0/10	0/8
Every day × 5, Days 14-18	200-81.9	128	640	20.9	3.0	4/10	1/10	3/8
		102.4‡	512	22.0	4.1	3/10	0/10	0/8
		81.9	409.5	17.4	−0.5	0/10	0/10	0/8
Every day × 9, Days 14-22	160-65.5	102.4	921.6	26.7	8.8	1/10	5/10	3/8
		81.9‡	737.1	20.8	2.9	1/10	1/10	0/8
		65.5	589.5	18.0	0.1	0/10	0/10	0/8
Every 7 days × 2, Days 14 and 21	250-102.4	200	400	38.6	20.7	4/10	5/10	0/8
		160‡	320	19.4	1.5	8/10	0/10	0/8
		128	256	21.0	3.1	2/10	0/10	0/8
Every 14 days × 2, Days 14 and 28	250-102.4	200	400	22.0	4.1	6/10	3/10	0/8
		160‡	320	26.8	8.9	5/10	0/10	0/8
		128	256	22.5	4.6	4/10	0/10	0/8

*Experimental formulation used: freeze-dried powder containing 250 mg of flavone acetic acid and sufficient sodium hydroxide to adjust pH to 7-9 when reconstituted with 5 ml of sterile water. Further dilution was made with saline.

†Excludes drug deaths and tumor-free survivors.

‡Optimal dose.

In contrast to its activity against the Colon 38 tumor, flavone acetic acid demonstrated only moderate activity against two murine leukemias. In the initial experiment against the ip implanted P388 leukemia, no activity [increase in life span (ILS) < 20%] was observed following ip administration of the drug on Days 1-9. In a later experiment, moderate P388 activity (ILS = 49%) was observed when the same daily treatment schedule was used, but no activity was noted with a single treatment. In the ip implanted L1210 leukemia model, flavone acetic acid also was not effective following a single injection (ILS < 25%), but demonstrated moderate activity (ILS = 47% and 35%) in two of three experiments following nine daily treatments.

DISCUSSION

The murine Colon Adenocarcinoma 38 has been refractory to most compounds screened against it since 1976 (2). Of 1085 compounds selected for testing against Colon 38 mainly on the basis of some level of activity against the P388 leukemia, only 1.4% (excluding analogs of main classes of clinical antitumor agents) inhibited growth of the Colon 38 tumor by 90%-100% (2). A later analysis (J. Plowman, unpublished observations) showed that 39 of 1708 compounds (2.3%, including analogs) demonstrated activity against the colon tumor. Flavone acetic acid ester was one of the few novel agents identified by the colon tumor and was selected for development to clinical trial as part of a prospective study to determine whether compounds identified by preclinical solid tumor models are more effective against human solid tumors than agents identified by experimental leukemia models. Although the flavone acetic acid ester has entered phase I clinical trials in the United Kingdom (7), it has been replaced by flavone acetic acid in the DCT Drug Development Program. The acid demonstrated equivalent Colon 38 activity to that of the ester on ip administration, but in contrast to the ester, retained its activity and potency on iv administration. Phase I trials with the acid should start in late 1985.

It is likely that the solid tumor activity of the flavone acetic acid would have been missed by the NCI 1976-1982 screening experiment except for drug development based on the ester lead compound, since initial testing of the acid against the P388 leukemia demonstrated no activity. Although subsequent studies have shown some activity against both the P388 and L1210 leukemias, this activity appears insignificant compared to activity against solid tumors. In addition to the Colon 38 activity reported here, flavone acetic acid has been shown to inhibit the growth of a broad spectrum of experimental murine solid tumors (T. H.

Corbett, personal communication).

In mice, the therapeutic efficacy of flavone acetic acid is observed when the sites of tumor implantation and drug administration are separated. The compound has a narrow therapeutic dosage range and antitumor activity is decreased if bolus treatments are closely spaced, a finding that can be explained by the unusually slow plasma clearance of flavone acetic acid in mice and toxicity related to peak plasma levels (8). The mechanism of action of this agent, which appears to preferentially inhibit the growth of solid tumors, is not understood at the present time.

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Neurotransmitter Receptor Binding Studies Predict Antiemetic Efficacy and Side Effects[1,2]

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Radioligand binding studies were used to analyze the interaction of antiemetics with central dopamine D_2 and alpha-adrenergic$_1$ receptors. The affinity of antiemetics for dopamine D_2 receptors labeled by ^{3}H-spiperone significantly correlated with clinically effective drug doses ($r = 0.92$; $P < 0.01$). Furthermore, the relative inhibition of alpha-adrenergic$_1$ receptors as measured by ^{3}H-WB 4101 binding predicts the clinical side effects of sedation and orthostatic hypotension. Neurotransmitter receptor binding analysis provides a rapid and sensitive technique for measuring antiemetic potency as well as associated side effects. [Cancer Treat Rep 70:637–641, 1986]

Nausea and vomiting are two of the most untoward side effects of cancer chemotherapy (1–3). To date, a variety of pharmacological agents have been used in the treatment of chemotherapy-induced nausea and vomiting (4–8). In particular, neuroleptics are commonly used therapeutic agents. Theoretically, their efficacy derives from a blockade of dopamine receptors, presumably in the region of the area postrema (9). However, neuroleptics vary in their clinical efficacy and, in addition, are frequently associated with severe side effects such as sedation and orthostatic hypotension.

Radioligand binding studies provide a rapid and sensitive measure of drug potencies at central neurotransmitter receptor binding sites (10,11). For example, the potency of neuroleptics in blocking dopamine D_2 receptors correlates significantly with their antipsychotic activity (12). In addition, drug affinity for alpha-adrenergic$_1$ receptors has been used as a predictor of clinical sedation and orthostatic hypotension (13,14). We therefore examined a series of ten antiemetics and three neuroleptics at both dopamine D_2 receptors labeled by ^{3}H-spiperone and alpha-adrenergic$_1$ receptors labeled by ^{3}H-WB 4101. We now report that radioligand binding studies can be used as a rapid biochemical screen of antiemetic efficacy and side effects.

MATERIALS AND METHODS

Receptor binding assays were performed according to the methods of Peroutka et al (13). Briefly, adult rat brains were purchased from Pel-Freez Biologicals (Rogers, AR) and stored at −20°C. The brains were defrosted and the various anatomical regions were dissected as needed immediately prior to each experiment. Tissues were homogenized in 20 volume of 50 mM Tris-HCl buffer (pH 7.7 at 25°C) using a Brinkmann Polytron and then centrifuged at 49,000 × g for 10 minutes. The supernatant was discarded and the pellet resuspended in the same volume of Tris-HCl buffer prior to a second centrifugation at 49,000 × g for 10 minutes. The final pellet was resuspended in 80 volume of Tris-HCl buffer for ^{3}H-WB 4101 binding in the cortex or in 240 volume of Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ for ^{3}H-spiperone binding in the caudate.

Binding assays consisted of 0.1 ml of ^{3}H-ligand (final concentration of 0.5 nM ^{3}H-WB 4101 or 0.8 nM ^{3}H-spiperone), 0.1 ml of buffer or displacing drug, and 0.8 ml of tissue suspension. This concentration of ^{3}H-WB 4101 was used due to the recent observation of Norman et al (15) that higher concentrations of ^{3}H-WB 4101 (3 nM) also label 5-hydroxytryptamine$_{1A}$ receptors. Following incubation at 25°C for 30 minutes, the assays were rapidly filtered under vacuum through glass fiber filters (Schleicher and Schuell; #32 glass; Keene, NH) with two 5-ml washes using 50 mM Tris-HCl buffer. Radioactivity was measured by liquid scintillation spectroscopy in 7 ml of Aquasol (New England Nuclear; Boston, MA) at 54% efficiency. Specific binding was defined as the excess over blanks taken in the presence of 1 μM droperidol for ^{3}H-WB 4101 binding and 1 μM (+)-butaclamol for ^{3}H-spiperone binding. Generally, 75%–80% of the total ^{3}H-WB

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4101 binding and 60%–70% of the total ^{3}H-spiperone binding was specific.

Drugs were dissolved as follows: amitriptyline, trimethobenzamide, and metoclopramide in 50 mM Tris-HCl buffer; chlorpromazine and trifluoperazine in deionized water; droperidol, haloperidol, thiethylperazine, and fluphenazine were first dissolved in 1–3 ml of 95% ETOH and then diluted in buffer; and (+)-butaclamol, domperidone, pimozide, prochlorperazine, and spiperone were first dissolved in 0.01–1 ml of glacial acetic acid and then diluted in buffer.

Drugs were obtained from the following sources: ^{3}H-WB 4101 and ^{3}H-spiperone (19.8 Ci/mmol and 23.4 Ci/mmol, respectively; New England Nuclear), amitriptyline, chlorpromazine, and metoclopramide (Sigma Chemical Co, St Louis, MO); droperidol, domperidone, and spiperone (Janssen Pharmaceuticals, Piscataway, NJ); (+)-butaclamol (Research Biochemicals, Inc, Waltham, MA); trifluoperazine and prochlorperazine (Smith, Kline & French, Philadelphia, PA); thiethylperazine (Boehringer Ingelheim Ltd, Ridgefield, CT); and trimethobenzamide (Beecham Laboratories, Bristol, TN).

RESULTS

The affinities of antiemetic drugs for dopamine D_2 receptors in neuronal membranes were determined (table 1). Of the 13 drugs selected for analysis, spiperone and fluphenazine are the most potent agents at the dopamine D_2 receptor with affinities of 0.23 and 0.50 nM, respectively. Thiethylperazine, (+)-butaclamol, haloperidol, and droperidol are essentially equipotent with K_i values of 1–2 nM. Trifluoperazine is slightly less potent at this receptor (K_i = 2.3 nM). By contrast, pimozide, prochlorperazine, and domperidone have affinities of approximately 10 nM. Chlorpromazine (K_i = 21 nM) is approximately one order of magnitude less potent than trifluoperazine. Metoclopramide is significantly less potent at the dopamine D_2 receptor, with an apparent K_i value of 160 nM. The least potent agent is trimethobenzamide, with a K_i value of 640 nM.

Of the 13 agents analyzed, ten have been previously studied in clinical antiemetic trials. The average recommended clinical dose for each of these ten agents was obtained from the literature (table 1). As shown in figure 1, a significant correlation exists between the average recommended clinical dose and antiemetic potency at the dopamine D_2 receptor ($r = 0.92$; $P < 0.01$).

Antiemetic potency was also assessed at central alpha-adrenergic$_1$ receptors labeled by ^{3}H-WB 4101. In general, each of these agents also displays high affinity for this neurotransmitter receptor site. As shown in table 2, droperidol (K_i = 1.3 nM) is the most potent agent at the alpha-adrenergic$_1$ receptor. Drugs such as fluphenazine, haloperidol, spiperone, thiethylperazine, and chlorpromazine all display approximately 10 nM affinity for this receptor. By contrast, (+)-butaclamol, trifluoperazine, pimozide, and domperidone are approximately fivefold to tenfold weaker at the ^{3}H-WB 4101 binding site. Prochlorperazine is significantly less potent than these agents, with a K_i value of 200 nM. Finally, metoclopramide and trimethobenzamide are essentially inactive at the alpha-adrenergic$_1$ site, with K_i values > 10,000 nM.

A comparison of the relative inhibition of dopamine D_2 and alpha-adrenergic$_1$ receptors by chlorpromazine and prochlorperazine is shown in figure 2. As shown in figure 2A, prochlorperazine begins to inhibit the binding of ^{3}H-spiperone at the dopamine D_2 receptor at concentrations > 3 nM. By concentrations > 10 nM, approximately 50% of the specific ^{3}H-spiperone binding has been displaced by prochlorperazine. At 1000 nM, prochlorperazine completely inhibits the binding of ^{3}H-spiperone to the dopamine D_2 receptor. By contrast, prochlorperazine is less potent in inhibiting the binding of ^{3}H-WB 4101 to the alpha-adrenergic$_1$ receptor. No effect on the ^{3}H-WB 4101 binding is observed until concentrations > 100 nM are

TABLE 1.—Antiemetic interactions with dopamine D_2 receptors

Drug	Trade name	Recommended clinical dose (mg)*	Potency at dopamine D_2 receptor (K_i in nM)
Spiperone	—	—	0.23
Fluphenazine	Prolixin	1.5–2	0.50
Thiethylperazine	Torecan	10–20	1.1
(+)-Butaclamol	—	—	1.3
Haloperidol	Haldol	1–10	1.3
Droperidol	Inapsine	5–10	1.9
Trifluoperazine	Stelazine	1	2.3
Prochlorperazine	Compazine	10–25	6.8
Pimozide	Orap	—	7.8
Domperidone	Motilium	4–20	11
Chlorpromazine	Thorazine	10–300	21
Metoclopramide	Reglan	70–210	160
Trimethobenzamide	Tigan	200–250	640

* Clinical data were obtained from ref Nos. 3, 5, 8, and 19.

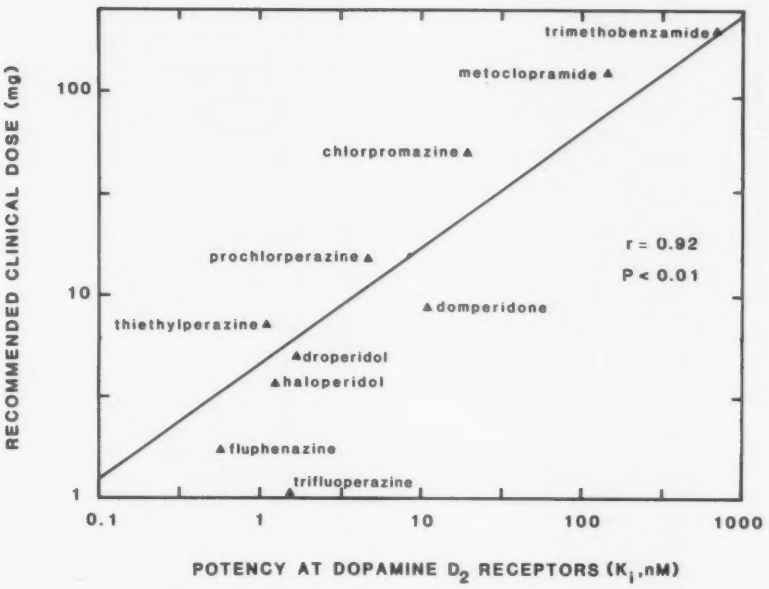

FIGURE 1.—Correlation between antiemetic affinity for dopamine D_2 receptors labeled by ^{3}H-spiperone and average recommended clinical doses.

achieved. At a concentration of approximately 500 nM, 50% of the specific alpha-adrenergic$_1$ binding is displaced. No residual binding remains in the presence of 10,000 nM prochlorperazine.

An inverse pattern of relative drug potency is observed with chlorpromazine (fig 2B). Chlorpromazine is most potent in inhibiting ^{3}H-WB 4101 binding to the alpha-adrenergic$_1$ receptor, with displacement first noted at 1 nM and becoming maximal at 1000 nM. Inhibition (50%) of alpha-adrenergic$_1$ receptor binding occurs at approximately 20 nM. Approximately tenfold higher concentrations of chlorpromazine are needed to achieve the same effect at the dopamine D_2 receptor labeled by ^{3}H-spiperone.

TABLE 2.—Antiemetic interactions with alpha-adrenergic$_1$ receptors

Drug	Potency at alpha-adrenergic$_1$ receptors (K_i in nM)	Ratio of K_i alpha-adrenergic$_1$: K_i dopamine D_2 *
Chlorpromazine	8.8	0.42
Droperidol	1.3	0.68
Domperidone	74	6.7
Pimozide	78	10
Haloperidol	14	11
Thiethylperazine	17	15
Fluphenazine	8.1	16
Trimethobenzamide	16,000	25
Prochlorperazine	200	29
Trifluoperazine	68	30
(+)-Butaclamol	45	35
Metoclopramide	10,000	62
Spiperone	25	110

* *From* table 1.

DISCUSSION

The major finding of the present study is that neurotransmitter receptor binding techniques can be used to screen for both the clinical efficacy and potential side effects of antiemetics. These data extend and confirm the observation of Peroutka and Snyder (11) that antiemetics display high affinity for dopamine D_2, histamine, and/or muscarinic cholinergic receptors. Theoretically, the antiemetic effects of neuroleptics derive from their blockade of dopamine receptors in the chemoreceptor trigger zone (16,17). In particular, dopamine D_2 receptors have been identified in the area postrema (9). These receptors can be directly labeled using ^{3}H-spiperone as a radioligand in neuronal membrane preparations. Since the affinities of antiemetics for these receptors significantly correlate with their effective clinical doses ($r = 0.92$; $P < 0.01$), these data confirm that the dopamine D_2 receptor mediates antiemetic actions.

The ability to predict antiemetic efficacy based on radioligand data has many practical implications. First of all, drugs such as spiperone, pimozide, and (+)-butaclamol are currently unavailable for clinical use in the United States. However, the data in the present study

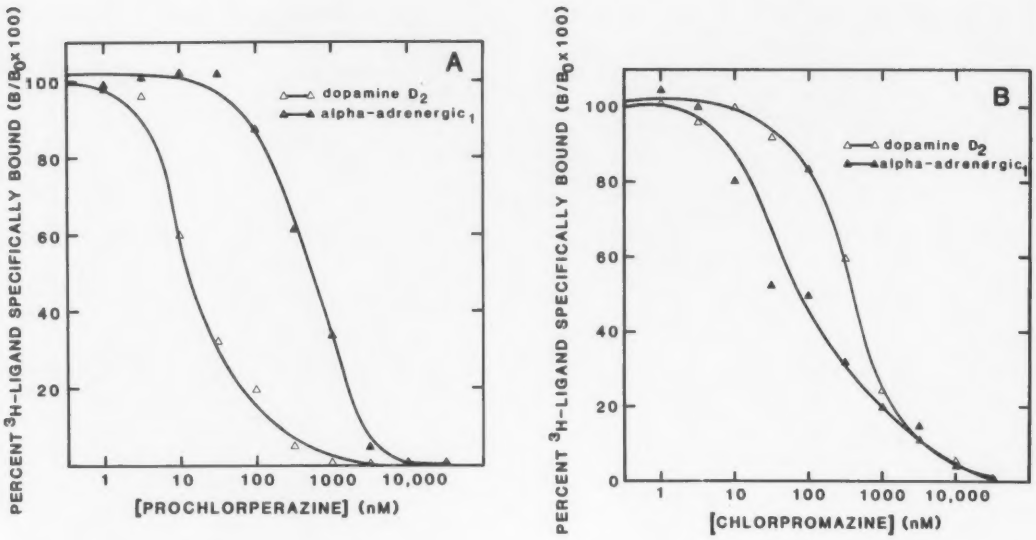

FIGURE 2.—Inhibition of dopamine D_2 receptors labeled by ^{3}H-spiperone and alpha-adrenergic$_1$ receptors labeled by ^{3}H-WB 4101. A (inhibition by prochlorperazine) and B (inhibition by chlorpromazine).

suggest that these agents should be potent antiemetics. Second, the potency of novel antiemetics at the dopamine D_2 receptor may be a useful predictor of effective doses in pilot clinical trials. Third, radioligand studies may be useful in determining the primary site of drug action. For example, the therapeutic efficacy of metoclopramide has been attributed to its effects on gastric motility (18), while the mechanism of action of trimethobenzamide is unclear (2-8). The current data suggest that dopamine receptor blockade plays a prominent, if not primary, role in the antiemetic effects of these two drugs.

At the same time, the interactions of drugs with alpha-adrenergic$_1$ receptors have been correlated with sedative and orthostatic hypotensive side effects (13,14). These side effects have also been noted with antiemetics. Clinical studies have shown that the incidence of orthostatic hypotension and sedation varies widely among antiemetics. For example, chlorpromazine and prochlorperazine are essentially equipotent antiemetics. However, the incidence of sedative and orthostatic side effects with chlorpromazine is far more frequent and severe than that observed with prochlorperazine (8,19).

The use of ^{3}H-WB 4101 to label the alpha-adrenergic$_1$ receptors appears to be a useful tool for the analysis of these effects. The relative potencies of drugs at alpha-adrenergic$_1$ and dopamine D_2 receptors may explain the variability of the side effects. For example, chlorpromazine is more than twice as potent at alpha-adrenergic$_1$ receptors than at dopamine D_2 receptors. At clinically effective antiemetic doses, dopamine D_2 receptors are theoretically blocked by chlorpromazine. At such concentrations, an even greater percentage of alpha-adrenergic$_1$ receptors are simultaneously blocked. By contrast, at concentrations of prochlorperazine at which a significant proportion of dopamine D_2 receptors are blocked (10 nM), only a small percentage of alpha-adrenergic$_1$ sites are blocked. Thus, the ratio of alpha-adrenergic$_1$ to dopamine D_2 affinities can be used as a measure of sedation and orthostatic hypotension. Based on these data, chlorpromazine and droperidol should be relatively sedative, whereas trifluoperazine and metoclopramide should be less sedating. These predictions have been confirmed by clinical experience (8,19-21).

Therefore, radioligand binding studies may provide a useful and accurate laboratory predictor of clinical antiemetic efficacy. In particular, binding studies could be used as a screening device for novel antiemetics that act through dopamine D_2 receptors. These techniques may also be applied to the study of antiemetics which act at histamine and muscarinic cholinergic receptors. The experiments could be performed rapidly and economically. Moreover, receptor binding studies can also be used to predict major side effects. Finally, the use of receptor binding assays in the analysis of antiemetic action may provide important information concerning the pathophysiology of nausea and vomiting in humans.

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Cisplatin and Radiation Therapy for Locally Advanced Squamous Cell Carcinoma of the Lung[1]

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A pilot study was initiated to test the safety and efficacy of the simultaneous administration of high-dose cisplatin and irradiation in patients with locally advanced squamous cell carcinoma of the lung. Cisplatin was administered at 100 mg/m² on Days 1 and 21 and was continued at 20 mg/m² once a week to the completion of radiation therapy. Irradiation was begun on Day 22 and was administered 5 days a week for 6 weeks at a rate of 200 cGy per day to a total of 6000 cGy to the primary site, using a shrinking field technique. Of the 13 patients so treated, all but one showed objective evidence of tumor regression according to chest x-ray. Six patients are still alive from 12 to 37 months after the start of treatment, including four who are asymptomatic and without apparent tumor and two with persistent local disease. Of the seven patients who died, four had metastatic disease (including one with local recurrence as well), one (who had been resistant to therapy) had persistent local disease, and two died too early to allow comment on efficacy (although autopsy in one case showed no evidence of locoregional tumor). This program is both active and tolerable, and deserves further study. [Cancer Treat Rep 70:643–645, 1986]

Several investigators have documented the radiopotentiating effects of cisplatin (CDDP) in cellular systems, and have found these effects to be preferential for hypoxic cells (1–4). Studies using CDDP and radiation therapy in the treatment of various human tumors have shown encouraging results, but no such study to date has dealt specifically with squamous cell carcinoma of the lung (SQCCL) (5,6).

The simultaneous use of radiation therapy (RT) and CDDP is attractive for a number of reasons. CDDP is cytotoxic per se and may kill malignant cells not only in the primary site but also in micrometastatic disease. CDDP is not generally believed to concentrate in normal tissues other than the kidney and liver, and therefore should not promote radiation toxicity in surrounding normal tissue (7,8). The common toxic effects of CDDP do not overlap with those of RT. Finally, CDDP is thought to be a radiopotentiator, enhancing the effect of RT when the two modalities are used together.

To test the hypothesis that a combined program of CDDP and RT can be both effective and tolerable, we treated 13 patients having localized unresectable SQCCL with high-dose CDDP and RT, with curative intent. The preliminary results are reported here.

PATIENTS AND METHODS

Entry criteria.—The study was limited to patients with pathologically confirmed unresectable SQCCL restricted to the primary tumor who had no prior history of malignant tumor other than non-melanoma skin cancer. Other criteria included: ipsilateral and/or contralateral hilar (N_1) or mediastinal (N_2) nodes, and ipsilateral or contralateral supraclavicular nodes; serum creatinine < 1.5 mg/100 ml; creatinine clearance > 60 ml/min; wbc count > 4000/μl; platelet count > 150,000/μl; anticipated survival > 2 mos; and Karnofsky performance > 40. Informed consent was obtained from all patients.

Cisplatin.—On Days 1 and 21, patients received 100 mg/m² of CDDP in 500 ml of normal saline (NS) by iv drip over 60 minutes. In the 5 hours prior to CDDP administration, 1000 ml of NS with 20 mEq of KCl was giv-

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en to induce urine output of 150 ml/hr at the time of infusion and for 12 hours thereafter. Thirty minutes prior to CDDP infusion, patients were given antiemetics, consisting in most cases of metoclopramide and dexamethasone. RT was begun on Day 22. On Day 28 and every 7 days thereafter to the completion of RT, patients were given 20 mg/m^2 of CDDP in 500 ml of NS by iv drip over 30 minutes in the outpatient unit. Adequate hydration prior to and for 12 hours following this infusion was encouraged. Modifications of all CDDP doses were made on an individual basis depending on hematologic and renal toxicity. CDDP was withheld if the serum creatinine was > 2.0 mg/100 ml, the platelet count was < 60,000/μl, or the wbc count was < 2000/μl. CDDP was given at 50% doses if the platelet count was between 60,000 and 100,000/μl or the wbc count was between 2000 and 3000/μl, and at 75% doses if the platelet count was between 100,000 and 125,000/μl or the wbc count was between 3000 and 4000/μl.

Radiation therapy.—RT was administered with a 4-MeV Varian linear accelerator, 80 cm source to axis distance using individualized poured blocks. The fields included the primary tumor with a 1.5-cm margin and the bilateral hilar, subcarinal, mediastinal, and supraclavicular lymph nodes. The dose rate was 180–200 cGy per day, 5 days per week, with both anterior and posterior fields being treated each day. A minimum of 4600 cGy was administered to the large field, with a 1400-cGy boost to the primary site and any other bulky nodal disease. A GE treatment-planning unit incorporating GE8800 computerized tomographic scans was used to outline fields that would keep the spinal dose within tolerable limits (4600 cGy). There was no calculated dose reduction to the spinal cord.

Response criteria.—Complete response (CR) was defined as the disappearance of all measurable and palpable tumor, response (R) was defined as any measurable or evaluable reduction of tumor volume, and progressive disease (P) was defined as an increase in size of measurable tumor during therapy or the development of metastatic disease. Survival, calculated from the date of diagnosis, was considered the major indicator of therapeutic effectiveness.

RESULTS

Thirteen patients, 12 males and one female, entered this study. Patient characteristics and survival statistics are shown in table 1. In all but one case, objective evidence of tumor regression was indicated by chest x-ray before changes consistent with radiation fibrosis obscured further documentation of therapeutic effectiveness. Six patients are alive between 12 and 37 months after the onset of therapy, including two with the appearance of persistent local tumor by x-ray and four who are asymptomatic and without apparent tumor. Of the seven patients who died, one (who had shown no response to treatment) failed with persistent local disease, three failed with distant metastases, one failed with both brain metastases and local recurrence, and two died too early to allow comment on local control.

All patients were able to complete the full RT course, despite interruptions of up to 13 days for mucositis (two patients), esophagitis (three), skin rash (one), and pneumonia unassociated with neutropenia (one). Mucositis, esophagitis, and skin rash were all grade 2 based upon a Radiation Therapy Oncology Group grading system of 1–4. There were no acute episodes of radiation pneumo-

TABLE 1.—Patient characteristics and survival statistics

Patient No.	Age (yrs)	Sex	Performance status	TNM stage	Treatment field size*	% CDDP	Response	Survival (mos)	Current status	Recurrent disease
1	59	F	70	$T_3N_2M_0$	19×11 → 10×6	88	R	2	Dead†	None
2	66	M	80	$T_3N_2M_0$	16×16 → 10×8	93	CR	3	Dead‡	None
3	62	M	80	$T_2N_2M_0$	17×12 → 17×9	86	CR	37	Alive	None
4	56	M	80	$T_3N_2M_0$	18×10 → 18×6	100	CR	15	Dead	Brain
5	70	M	80	$T_3N_0M_0$	16×10 → 7×8	79	R	15	Dead§	Bone
6	48	M	70	$T_3N_2M_0$	14×12 → 8×6	67	P	6	Dead	Local
7	62	M	90	$T_3N_0M_0$	18×12.5 → 10×10	77	CR	29	Alive¶	Local
8	52	M	80	$T_3N_2M_0$	15×10 → 13×10	93	R	11	Dead	Brain
9	67	M	90	$T_3N_2M_0$	18×10 → 18×7	55	CR	20	Alive	None
10	58	M	80	$T_3N_2M_0$	18×10 → 8×8	83	R	8	Dead	Bone Local
11	69	M	100	$T_3N_2M_0$	24×14 → 11×12	85	CR	14	Alive	None
12	70	M	80	$T_3N_1M_0$	23×14 → 20×10	67	R	12	Alive**	Local Brain
13	47	M	90	$T_3N_2M_0$	21×12 → 10×10	100	CR	24	Alive	None

*Numbers after arrow indicate "boost" volume.

†Death secondary to fatal gastrointestinal bleed while on heparin. Not believed to be treatment-associated (platelet count normal).

‡Death from fatal bleed resulting from large erosion into left pulmonary artery. Autopsy showed no evidence of locoregional tumor.

§Death secondary to pulmonary embolus.

¶Patient has had some shrinkage of tumor locally, but still has persistent local disease.

**Patient had initial shrinkage of tumor locally, but then progressed.

nitis, carditis, or Lhermete's syndrome.

Ten of the 13 patients received at least 75% of the calculated CDDP dosage. Nausea and vomiting were reasonably well handled by premedication, with most patients experiencing mild to moderate discomfort and none stopping therapy for this reason. Neutropenia occurred in four patients, but in no case did any patient's wbc count drop to < 3000/μl, although in two patients the platelet count was approximately 100,000/μl. Two patients developed mild transient elevations of BUN and creatinine, while one patient developed an increase of BUN and creatinine that lasted 5 weeks and required cessation of CDDP.

DISCUSSION

Our ongoing phase I-II study demonstrates that a combination of high-dose CDDP and RT can be given to patients having unresectable SQCCL without serious toxicity. Preliminary results also indicate potential activity from this combination in terms of objective tumor regression.

The most effective treatment to date, RT at 6000 cGy, has achieved local control in 50%-60% of patients (9-13). In this report, two of seven deaths were related to local recurrence; only two of six survivors showed local disease. Moreover, in one death from bleeding due to erosion into the left pulmonary artery, autopsy evidence of local tumor sterilization was found.

It is too early to predict the effect of this treatment on survival, which is the only certain objective parameter of tumor activity in this disease (14). However, as Cox et al (15) and Eisert et al (16) have pointed out, regional control significantly improves survival. Our preliminary results in this small number of patients suggest that CDDP may be both a radiopotentiator and an effective cytotoxic agent in SQCCL. We believe further investigation of this combination therapy on both local control and survival is warranted.

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Peptichemio in Advanced Breast Cancer: A Clinical Evaluation in 32 Patients[1]

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A clinical evaluation of peptichemio (40–45 mg/m²/day for 3 days every 3–4 weeks) was conducted in 32 patients with advanced breast cancer, 28 of whom were evaluable for both toxicity and response. The overall response rate was 18% (one complete remission and four partial remissions), with a median duration of 4 months (range, 2–6). The major side effects were cumulative myelotoxicity, phlebitis, mild nausea, and vomiting. A posttreatment heparin infusion was used to prevent phlebitis. [Cancer Treat Rep 70:647–649, 1986]

Peptichemio (PTC) is a peptide complex of *m*-L-phenylalanine mustard and was synthesized by De Barbieri et al (1) in 1966. Clinical evaluation of PTC was conducted in some European and American institutions, with significant responses in different types of malignancies (2–6). Grose et al (5) and Hug et al (7) have reported an overall remission rate of 32% in 56 patients with breast cancer, with a dose range between 20 and 75 mg/m²/day × 3 every 3–4 weeks. In our previous experience, 71 evaluable patients with solid tumors and hematologic malignancies underwent chemotherapy with PTC (60–80 mg/m² every 2 weeks). Sixteen of 71 patients had disseminated breast cancer. In this group, two of 16 patients achieved response (12%), while in the remaining patients no response was obtained (8).

The aims of this study are to evaluate the efficacy of PTC in disseminated breast cancer and to compare our previous clinical findings obtained from a dose schedule of 60–80 mg/m² every 2 weeks with the results achieved from a starting dose schedule of 40 mg/m²/day × 3, which was increased to 45 mg/m²/day in the patients in whom no severe myelotoxicity was observed. This schedule appeared in previous literature to be most appropriate for tolerance and antitumor activity.

MATERIALS AND METHODS

Thirty-two patients with disseminated breast cancer that had proven to be resistant to various chemotherapy combinations (doxorubicin, cyclophosphamide, methotrexate, 5-FU, carmustine, and mitomycin), hormonal agents (tamoxifen, medroxyprogesterone acetate, and aminoglutethimide), and radiotherapy were admitted to this study. Prior to entry in the study, all patients were removed from hormonal and other chemotherapeutic agents for a period of at least 4 weeks. Informed consent was obtained from each patient. Criteria required for admission to the study were the following: evaluable disease; Karnofsky performance status > 40; and expected survival > 3 months. A minimum of two cycles of chemotherapy were given to all patients, with a median of three courses (range, two to six). Response criteria according to International Union Against Cancer criteria were used (9). Durations of remission and survival were determined from the start of treatment. The drug schedule was the following: PTC at a dose of 40–45/mg/m²/day × 3, with each course repeated at 21-day intervals depending on bone marrow recovery. PTC was administered iv over 20–30 minutes after dilution in 100 ml of 5% dextrose in water. Before drug administration, clorfenamine (10 mg im) and betamethasone (8 mg iv) were injected to prevent allergic reactions. No reduction in the dose was considered if thrombocytopenia and/or granulocytopenia occurred. When there was a leukocyte count < 3000/mm³ and/or a platelet count < 100,000/mm³, a cbc was repeated every 4 days until the values had sufficiently recovered for administration of the next dose.

RESULTS

Thirty-two patients were entered in the study. Four patients were not evaluable; two were lost to follow-up during the first cycle of chemotherapy (probably due to the distance from our unit); one refused treatment because she was concerned about an allergic reaction during the first cycle of chemotherapy; and one received medroxy-

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TABLE 1.—Characteristics of responding patients*

Patient No.	Age (yrs)	Prior treatment	Site of metastases	Type of response	Duration of remission (mos)
1	56	CT + RT	Nodes, skin	CR	6
2	49	CT	Lung, pleura	PR	3
3	48	CT + HT	Chest wall, nodes	PR	4
4	62	CT + RT	Nodes, skin	PR	2
5	59	CT + HT	Chest wall, nodes	PR	5

*CR = complete response; PR = partial response; CT = chemotherapy; HT = hormonal therapy; and RT = radiotherapy.

progesterone acetate concomitantly with PTC (and was excluded from the study). Therefore, 28 patients were evaluable. Patient characteristics and sites of disease are shown in tables 1 and 2. A total of 97 courses of PTC were administered at a median dose of 40 mg/m^2/day × 3. The overall response rate was 18% (five responses among 28 patients), with one patient achieving complete remission and four achieving partial remission. Four patients had stable disease. The median duration of response was 4 months (range, 2-6). The response sites were viscera and soft tissues. Bone lesions failed to show any evaluable response, as indicated by x-ray and bone scan, concentrations of urinary calcium, phosphorus, blood alkaline phosphatase, and urinary hydroxyproline.

Toxicity

Cumulative myelosuppression was the major drug-related toxic effect. Neutropenia, of various degree, was observed in all patients receiving treatment, with the nadir usually encountered in the second week. Thrombocytopenia was also present, but at a lesser degree, with the nadir between the second and the third week. Myelosuppression was severe in heavily pretreated patients. In 20% of the patients, it was necessary to lengthen the treatment interval because of cumulative myelosuppression (usually after three cycles of PTC). No infections or hemorrhagic complications were observed. The major nonhematologic toxicity was venous thrombosis at the site of injection, often resulting in phlebosclerosis and sometimes in chronic edema of the limb. We tried to prevent this disadvantage by a drip administration of heparin (4000 IU) diluted in 250 ml of 5% glucose through the same line after PTC administration. We observed an incidence of local phlebitis of 5%/course by administering heparin at this dose. Twenty percent of the patients experienced a pruriginous, maculopapular rash at the site of infusion and along the vein perfused. Nausea and vomiting were, as a rule, mild. Alopecia was complete in seven patients and partial in the others.

TABLE 2.—Disease distribution and response site

Site	Incidence (%)	No. of patients responding (%)
Soft tissue	83	6 (21)
Bone	35	—
Liver	11	1 (3)
Lung	20	1 (3)
Pleura	20	1 (3)
Skin	40	2 (7)

DISCUSSION

In the study of Grose et al (5), an improvement of performance status is also considered in the evaluation of the response; using conventional criteria, the objective response rate achieved is only 14%, with a dose schedule of 45 mg/m^2 × 3 every 3-4 weeks. Considering the advanced stage of the disease and the extensive prior treatment of our patients, the observed response rate of 18% appears encouraging. In addition, all patients had been previously treated with an alkylating agent (cyclophosphamide) and non-cross-resistance of PTC with cyclophosphamide is consequently suggested. No advantage has been achieved by administering PTC in a "fractioned" schedule in comparison to the single-dose schedule to prevent phlebitis (36% in our study versus 19% with single dose).

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Vindesine and Mitomycin in the Treatment of Advanced Non-Small Cell Lung Cancer: A Southeastern Cancer Study Group Trial[1,2]

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Vindesine (VDS) has previously been reported to have a response rate of 20%–25% in non-small cell lung cancer (NSCLC) but without improvement in patient survival (1). The addition of high-dose cisplatin has been reported to increase the response rate and may improve survival, but it requires hospitalization (2). Mitomycin (MMC), when administered at a high dose by bolus on an intermittent schedule, has been reported to have single-agent activity in NSCLC comparable to that of vindesine (3). The dose-limiting toxic effect of MMC, thrombocytopenia, is complementary to the neurotoxicity and neutropenia of VDS (1). Both drugs can be given to outpatients. Based on these considerations, the Southeastern Cancer Study Group (SEG) conducted this trial between 1981 and 1984.

MATERIALS AND METHODS

Patients were eligible for treatment if they had pathologically proven NSCLC that was incurable and measurable; had normal renal, hepatic, and bone marrow function (unless tumor-related abnormalities were present); had an expected survival of at least 6 weeks; and had given written informed consent.

VDS was administered at a dose of 3 mg/m^2 by iv bolus on Day 1 and weekly for 6 weeks. MMC was administered at a dose of 20 mg/m^2 (15 mg/m^2 for patients having previous radiation therapy) by iv bolus on Day 1. On Day 43, patients were evaluated for response. Those having stable or responding disease were given VDS (3 mg/m^2) every other week and MMC (15 mg/m^2) every 6 weeks. MMC dose was attenuated on the basis of nadir platelet count and both platelet and wbc counts at the time of scheduled administration. VDS dose was attenuated on the basis of hematologic and neurologic toxicity at the time of scheduled administration, as previously described by Gralla et al (2). Toxicity was rated according to standard criteria (4). Patients were considered evaluable for response if they were in the study for 6 weeks (or less with documented disease progression). Response to therapy was defined as follows: *complete response (CR)*—the complete disappearance of all evidence of disease, including physical, radiographic, and biochemical; *partial response (PR)*—at least a 50% reduction in tumor size as determined by the products of the perpendicular diameters of measurable disease, without the appearance of new disease outside the central nervous system; *stable disease*—neither response nor progression; and *progressive disease*—at least a 25% increase in tumor size or appearance of new disease outside the central nervous system.

RESULTS AND DISCUSSION

A total of 130 patients were enrolled in this study, with 113 (87%) fully evaluable. This large number was enrolled to permit evaluation of subpopulations, particularly those having prior radiation therapy and, therefore, a lower dose of MMC. Among those patients not evaluable for response, eight died of unrelated illnesses before completing the first cycle of therapy, three refused therapy, and six were judged ineligible for the study.

Among the 113 fully evaluable patients, there were five CRs and 33 PRs (34%), with a median duration of 12 weeks. Patient characteristics in relation to response are shown in table 1. Low performance status was associated with poor response, but prior radiation therapy was not.

The 34% response rate with MMC and VDS appears superior to that with single-agent VDS (1). None of the single-agent VDS responses were CRs, compared with a 4% CR rate in this trial. The combination of MMC and VDS appears to have a response rate comparable to that achieved with combination of VDS and cisplatin (2).

The median survival for all 127 patients given therapy in this trial was 23 weeks, which is not different from

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TABLE 1.—Patient characteristics and response to MMC + VDS

Characteristic	No. of patients (%) Total	CR + PR	95% confidence limit (%)	*P* value
No prior irradiation	83	29 (35)	25-46	0.66
Prior irradiation	30	9 (30)	15-50	
Adenocarcinoma	44	11 (25)	14-41	0.08
Squamous cell carcinoma	47	21 (45)	30-60	
Large cell carcinoma	22	6 (27)	12-50	0.19
Male	86	27 (31)	22-42	0.48
Female	27	11 (41)	23-61	
Extensive disease*	77	24 (31)	21-43	0.52
Limited disease	36	14 (39)	24-56	
< 10% weight loss	60	23 (38)	26-52	0.32
⩾ 10% weight loss	53	15 (28)	17-43	
⩾ 80% PS†	78	31 (40)	29-51	0.053
< 80% PS†	35	7 (20)	9-51	

*By Veterans Administration Lung Study Group (VALSG) criteria.
†Karnofsky performance status.

that reported by the VALSG for a similar population of patients treated with supportive care only (5). Interpreting these data is hazardous, since factors unrelated to treatment may alter survival.

Toxic effects, as shown in table 2, were predominantly bone marrow suppression and peripheral neuropathy; 53% of patients had severe to life-threatening myelosuppression, which was transient in most patients. There was, however, one death from infection related to neutropenia. Despite the use of pulse pharmacologic doses of MMC, severe thrombocytopenia was infrequent. Pulmonary toxicity was seen in seven patients.

We conclude that the combination of VDS and MMC is active in NSCLC. The apparent lack of survival benefit for the population treated with VDS and MMC, when compared with untreated historical controls, is disconcerting but not definitive. This issue will be addressed in a randomized trial to be conducted by the SEG, which will compare the combinatin of MMC and VDS with cisplatin and VDS and with minimal chemotherapy.

TABLE 2.—Maximum drug toxicity exhibited by evaluable patients receiving MMC + VDS*

Toxic effect	No. of patients evaluated	Degree of toxicity† 1+	2+	3+	4+
Hematologic					
Wbcs	119	21 (18)	36 (30)	35 (29)	9 (8)
Neutrophils	118	11 (9)	17 (14)	33 (28)	30 (25)
Platelets	120	14 (12)	16 (13)	8 (7)	2 (2)
Hemoglobin	117	32 (27)	35 (30)	2 (2)	2 (2)
Hemorrhage	120	1 (1)			
Infection	119	2 (2)	1 (1)	1 (1)	1 (1)
Other					
Creatinine	102	2 (2)	1 (1)		
Nausea and vomiting	120	25 (21)	18 (15)	9 (8)	
Abdominal cramps	121	8 (7)	2 (2)	1 (1)	
Stomatitis	121	1 (1)	2 (2)	1 (1)	
Diarrhea	120	3 (3)	1 (1)	1 (1)	

*Nos. vary due to availability of data.
†Values = No. of patients (%).

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Continuous-Infusion Doxorubicin in the Treatment of Primary Hepatic Malignancies of Childhood[1,2]

Joseph P. Neglia* and William G. Woods[3,4]

Five children with primary hepatic malignancies were treated with continuous infusions of doxorubicin administered as a single agent every 3–4 weeks. Four of five children showed positive response to therapy, manifested by decreasing tumor size and/or tumor markers; the fifth child had stable disease for 4 months. Side effects included mild nausea and vomiting and myelosuppression. No evidence of cardiotoxicity was seen with cumulative doses up to 720 mg/m^2. [Cancer Treat Rep 70:655–657, 1986]

Doxorubicin has been found to be useful in a wide range of hematologic and soft tissue malignancies of childhood, including acute lymphocytic and nonlymphocytic leukemia, rhabdomyosarcoma, neuroblastoma, and Ewing's sarcoma (1). As a single agent it has also been demonstrated to be effective in the treatment of childhood hepatic neoplasms. Tan et al (2) reported cumulative data on 11 children with hepatoblastoma treated with iv bolus doxorubicin as a single agent at various centers. Five children responded with either a complete or a partial remission. Another study demonstrated marked reduction of primary tumor size in seven of eight children with either hepatoblastoma or hepatocellular carcinoma treated preoperatively with doxorubicin-containing regimens. Four of these previously unresectable tumors were then completely resected (3).

Side effects of doxorubicin administration include alopecia, nausea and vomiting, myelosuppression, and irreversible cardiotoxicity. The severity of the cardiotoxicity has led to the recommendation that the cumulative dose of doxorubicin not exceed 550 mg/m^2 (4). Recent reports, however, have demonstrated that adults treated with continuous 48- or 96-hour iv infusions of doxorubicin were able to tolerate significantly higher cumulative doses of the drug without any loss of antitumor activity and had less cardiotoxicity than a control group treated with conventional bolus injections (5). To our knowledge no similar trials have been conducted in pediatric patients. We have now used a 96-hour infusion of doxorubicin as a single agent to treat five children with primary hepatic malignancies, including one child who received the agent after undergoing liver transplantation.

MATERIALS AND METHODS

Five patients with hepatic malignancies, from 6 months to 10 years of age, were treated with continuous infusions of doxorubicin (table 1). Three were diagnosed with hepatoblastoma and two with hepatocellular carcinoma. In all patients, disease either was unresectable at time of presentation or had been partially resected. Patient 5 had received prior treatment with doxorubicin administered as a bolus. Patient 3 was diagnosed with hepatocellular carcinoma at the time of liver transplantation for hereditary tyrosinemia.

Doxorubicin was administered continuously for 96 hours via Hickman catheters with standard hospital infusion pumps. The dosage was 90 mg/m^2/course but was adjusted to 3 mg/kg/course in children weighing < 10 kg, to compensate for their large surface area relative to the ability of their livers to metabolize chemotherapeutic agents (6). The dosage for Patient 3 was reduced to 2.4 mg/kg/course because of the concurrent immunosuppressive therapy she was receiving after liver transplantation.

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RESULTS

Complete remission of disease was seen in two patients. Both of these children underwent "second-look" surgical procedures which revealed no evidence of disease after two courses of therapy. Patient 2 remains free of disease, with normal serum alpha-fetoprotein (AFP) levels at 10 months off therapy. Disease recurred in Patient 1 at 5 months after the second-look procedure.

Partial responses were achieved in two patients. Patient 4 had marked regression of pulmonary metastases and declining AFP levels through four courses of continuous doxorubicin, after which the AFP began to rise. Her therapy was changed to cisplatin after the seventh course of doxorubicin; a ^{131}I-anti-AFP antibody scan performed at that time confirmed the presence of active tumor in the left lung and suggested the possibility of recurrence in her liver. Surgical re-evaluation confirmed the presence of active tumor only in the left lung. She has now completed therapy with etoposide and has normal AFP levels following resection of the remaining tumor. Patient 5 had responded to conventional doxorubicin therapy, but after 135 mg/m^2 her tumor was still believed to be unresectable and she was experiencing numerous chemotherapy-related problems. She was withdrawn from therapy at that time but later presented to our institution because of worsening disease. She tolerated two courses of continuous doxorubicin very well, with minimal nausea and no stomatitis. AFP levels fell from 310,000 IU/ml to 24,640 IU/ml, and surgical resection was attempted. The surgical margins were reported to be free of tumor; however, postoperative complications prevented any further chemotherapy, and the patient died of these complications with recurrent disease 3 months from the time of surgery.

Patient 3, a 14-month-old female with hereditary tyrosinemia, was found to have hepatocellular carcinoma with massive extension into the hepatic veins at the time of liver transplantation. Postoperatively the surgical margins were found to be involved by tumor, and treatment with reduced doses of continuous doxorubicin was undertaken. Serum AFP levels fell postoperatively and remained stable for 3 months after the initiation of therapy. Re-evaluation performed because of rising serum AFP levels confirmed the presence of hepatocellular carcinoma in the transplanted liver as well as in the lungs and colon. All therapy has since been discontinued.

Toxicity

All patients were evaluated for evidence of cardiac toxicity clinically and by radionuclide left ventricular ejection fraction (LVEF). No patient had any clinically evident cardiac failure or significant reduction of the LVEF, although only two of our patients received > 550 mg/m^2 of doxorubicin.

Myelosuppression was seen in all patients. However, in all patients but one, bone marrow recovery permitted a 3-4-week dosing interval. No deaths occurred secondary to infection, but some of the children were hospitalized for fever while neutropenic. Patient 1 experienced severe pancytopenia following both courses of doxorubicin. This was believed to be due in part to delayed excretion of doxorubicin secondary to hepatocannilicular obstruction (direct bilirubin of 6.7 mg/dl at the time of her first course) and to hypersplenism secondary to portal hypertension. Her direct bilirubin had fallen to 4.3 mg/dl prior to the second course of doxorubicin, which was reduced by 20%. Hematopoietic recovery was again prolonged, and a bone marrow examination performed 2 months

TABLE 1.—Patient characteristics*

Patient No.	Age	Sex	Prior therapy	Diagnosis and disease status at initiation of therapy	Response	Cumulative dose (mg/m^2)	Current status
1	10 yrs	F	None	Hepatocellular carcinoma, massive liver	CR	170	Died. Recurrent progressive disease after trials of cisplatin and AZQ, 16 mos after diagnosis
2	6 mos	M	None	Hepatoblastoma, microscopic liver	CR	720	Alive. Off therapy 10 mos; NED
3	14 mos	F	None	Hepatocellular carcinoma, microscopic liver	SD	470	Alive. Off therapy with progressive disease 14 mos after diagnosis
4	16 mos	F	None	Hepatoblastoma, multiple pulmonary metastases	PR	630	Alive. NED. After therapy with cisplatin, surgical resection, then etoposide
5	2 yrs	F	Bolus DOX	Hepatoblastoma, massive liver	PR	315	Died. Postoperative complications with progressive disease 5 mos after initiation of continuous DOX

* CR = complete response; PR = partial response; SD = stable disease; NED = no evidence of disease; DOX = doxorubicin; and AZQ = diaziquone.

after the second course of therapy showed marked hypocellularity without evidence of tumor. Hypocellularity remained on repeat examination 4 months later. The patient's tumor recurred before any further chemotherapy was given.

Nausea, vomiting, and stomatitis were minimal or absent in all patients. No complications of the doxorubicin infusions occurred.

DISCUSSION

The limitations of doxorubicin therapy have historically been myelosuppression and cardiotoxicity. The use of prolonged infusions of doxorubicin has been well documented by several observers to reduce cardiotoxicity in adults (5,7,8), but no similar trials have been done with children. Our experience supports these observations, in that no objective or subjective evidence of cardiotoxicity was seen in any of these pediatric patients, although only two received > 550 mg/m^2 of doxorubicin. Severe pancytopenia was seen in one patient; however, her treatment course was complicated by hypersplenism and obstructive jaundice. Though no response to therapy could be documented in our patient who received therapy after liver transplantation, no unusual complications occurred during her treatment.

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Possible Mitoxantrone-Induced Amenorrhea[1,2]

Todd D. Shenkenberg* and Daniel D. Von Hoff[3]

A patient with adenoid cystic carcinoma was treated with mitoxantrone at a dose of 12 mg/m² every 3 weeks. After the fifth dose, she developed amenorrhea accompanied by vasomotor instability (hot flashes). Subsequent serum gonadotropin and estradiol levels confirmed the postmenopausal state. The mechanism of mitoxantrone-associated amenorrhea is most likely due to direct toxic effects on the ovary, as is seen with other forms of chemotherapy. Ovarian dysfunction with mitoxantrone has not been previously reported. The important consequences of chemotherapy-induced ovarian failure are described. This toxic effect may be more frequently described as the drug becomes more widely available. [Cancer Treat Rep 70:659–661, 1986]

Mitoxantrone is a recently developed anthraquinone that is a potent DNA-reactive cytotoxic drug. It has significant activity in numerous animal tumor model systems as well as in human breast carcinoma, lymphoma, and leukemia (1,2).[4] A usual dose of mitoxantrone is 12–14 mg/m² repeated every 21–28 days.[4] The dose-limiting toxic effect of mitoxantrone is myelosuppression, which is of short duration and rapidly reversible. Toxic effects reported include occasional alopecia, nausea and/or vomiting, stomatitis, and bluish-green discoloration of the urine and serum (2). Amenorrhea, a common sequela of other forms of chemotherapy, has not been previously reported with mitoxantrone.

CASE REPORT

A 33-year-old white female underwent a right radical maxillectomy for an adenoid cystic carcinoma in October 1977. She received irradiation (5000 rads to the maxilla and 5000 rads to right cervical nodes) postoperatively. Forty-four months later (at age 37) she had a routine follow-up chest x-ray that revealed multiple nodules which were biopsied and found to be recurrent adenoid cystic carcinoma. At the time of recurrent disease the wbc count was 6200/mm³ with normal differential, the hemoglobin was 12.2 g/dl, and the platelet count was 268,000/mm³. SMA-18 was normal and CEA was 15 ng/ml. The patient had regular menses and was receiving no hormones, oral contraceptives, or other drugs. Menarche was at age 14, and she has no children.

She was begun on a Southwest Oncology Group Study evaluating mitoxantrone at a dose of 12 mg/m² (20 mg in this patient) iv every 3 weeks. Fourteen weeks after starting mitoxantrone (at age 39), the patient became amenorrheic and noted the onset of hot flashes (total mitoxantrone dose, 60 mg/m² = 100 mg). She had a thorough gynecologic examination which was normal except for atrophic vaginitis. She was not pregnant. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were determined (table 1). She was taken off study 8 months after her initial response to chemotherapy. She received no other chemotherapy prior to mitoxantrone. Subsequently, she received cisplatin and later vincristine, doxorubicin, and cyclophosphamide. Her menopausal symptoms have continued and subsequent serum LH and FSH determinations are still in the menopausal range (table 1). She is alive on no treatment and is asymptomatic with steadily enlarging pulmonary nodules on chest x-ray.

DISCUSSION

Ovarian dysfunction associated with mitoxantrone has not been previously reported. The patient described had normal menstrual periods prior to therapy and with therapy became amenorrheic with symptoms of vasomotor instability. The elevated levels of serum LH and FSH and the depressed level of serum estradiol further support ovarian failure as the etiology. Although there is no direct evidence (such as ovarian biopsy), it is likely the pa-

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TABLE 1.—Relationship of mitoxantrone to amenorrhea

Treatment No. (dose)	Dose (mg/m^2)	Date	FSH, IU/ml (menopausal 31-205)*	LH, IU/ml (menopausal 30-154)*	Estradiol, pg/ml (menopausal 5-18)*	Comments
Pretreatment	12	6/4/81	—	—	—	Normal menses; granulocytopenia with 3rd course
1		7/30/81	—	—	—	
2		8/20/81				
3		9/10/81				
4	12	10/8/81	—	—	—	Normal menses
5		10/29/81				
Chemotherapy withheld		11/19/81	—	—	—	New onset of amenorrhea; total cumulative dose of mitoxantrone, 60 mg/m^2 = 100 mg
6	12	12/3/81	135	121	13.1	Amenorrhea; normal gynecologic examination except atrophic vaginitis
7	10	12/29/81	—	—	—	Amenorrhea; hot flashes
8		1/28/82				
9	10	3/11/82	128	115	13	Amenorrhea; hot flashes
Off study		7/1/82	—	—	—	Off study
Off study		8/26/82	161	111	14.8	Amenorrhea
Cisplatin (1 course)		10/19/82	—	—	—	Amenorrhea; progressive disease after 1 course
Vincristine		5/19/83	—	—	—	Amenorrhea; no response after 3 courses
Doxorubicin		6/23/83				
Cyclophosphamide		7/15/83				
Off study		12/6/84	94	120	0	Amenorrhea
Off study		10/10/85	—	—	—	Amenorrhea

* Values in parentheses = normal range for postmenopausal women.

tient's amenorrhea was induced by mitoxantrone. The mechanism of mitoxantrone-associated amenorrhea is most likely due to a direct toxic effect on the ovary with primary ovarian dysfunction, as is seen with other forms of chemotherapy (3).

Amenorrhea associated with chemotherapy for malignant disease has, until recently, received little attention. With the use of busulfan for chronic myelogenous leukemia, amenorrhea was frequently seen as a side effect (4). Numerous studies of adjuvant chemotherapy for breast cancer have shown the relationship of age to the development of amenorrhea (5,6). Koyama et al (7) reported amenorrhea in all patients ≥ 40 years of age who received a mean total dose of 5.2 g of cyclophosphamide compared to 9.3 g in younger patients. Likewise, patients treated with cyclophosphamide for nonmalignant disease had amenorrhea at a mean age of 29.6 years (7). Rose and Davis (6) showed a direct effect of chemotherapy on the ovaries by chemotherapy with decreased plasma estrogen and increased LH and FSH, which progressed with time.

The onset of chemotherapy-induced amenorrhea was confirmed by Chapman (8) in patients with Hodgkin's disease treated with mechlorethamine, vinblastine, procarbazine, and prednisone. She found that ovarian dysfunction was age- and dose-related (9). Ovarian biopsy demonstrated loss of follicles. Older women were more susceptible to the development of amenorrhea as were women treated with higher doses of chemotherapy.

There are many consequences of chemotherapy-induced amenorrhea in patients. Ovarian failure in young women leads to early osteoporosis, decreased reproduction, sexual dysfunction due to dyspareunia and loss of libido, and disruption of partnerships. Vasomotor instability may cause diagnostic confusion since it mimics sweats associated with active lymphoma (8).

Mitoxantrone is a useful new antineoplastic agent. Patients tolerate it well, with myelosuppression being the most frequent side effect. We have described the occurrence of ovarian failure during treatment with mitoxantrone. This toxicity may be more frequently reported as the drug becomes more widely available.

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Clinical Toxicity of Low-Dose Isotretinoin[1,2]

Libby Edwards, David S. Alberts,* and Norman Levine[3]

Although vitamin A has been known for many years to play an integral part in the normal growth of epithelium, the introduction of less toxic synthetic analogs has expanded the potential for use of this group of drugs in human disease. Isotretinoin (13-*cis*-retinoic acid), the only synthetic retinoid commercially available in the United States, has proven to be an active agent in the treatment of epithelial cancers (1-3) and mycosis fungoides (4). In addition to its activity against established cancers, considerable interest has been generated in the use of this synthetic compound as a chemopreventive agent. Administration of isotretinoin for this purpose requires long-term ingestion of the retinoid by patients at high risk for developing cancers. In these subjects without overt disease a high incidence of side effects is unacceptable. Our present study examined the clinical toxicity of isotretinoin at a low dose which may be appropriate for chemoprevention trials.

METHODS

Five male and five female healthy volunteers between 21 and 50 years of age were selected for this study. A baseline evaluation included a history and physical examination, a blood cell count, and screening blood chemistries including liver functions and fasting blood lipids. Volunteers then received isotretinoin (10 mg orally each day for 9 months), which supplied them with an effective dose of 0.11-0.14 mg/kg/day.

History and physical examinations and laboratory tests were repeated regularly during the 9-month period. Pharmacokinetic studies of isotretinoin and its metabolite, 4-oxo-13-*cis*-retinoic acid, were also performed and will be reported elsewhere.

Toxicity was judged to be present when either the subject or the examiner noted a change from pretreatment status. The level of toxicity was graded according to a clinical toxicity scale developed at our institution.

RESULTS AND COMMENT

In this study, all ten healthy volunteers who received isotretinoin (0.11-0.14 mg/kg/day orally for 9 months) had toxic reactions. Two subjects discontinued the drug, one because of joint and bone pain and the other because of general discomfort from many different symptoms. No serious toxicity as evidenced by physical signs of laboratory evaluation occurred (table 1).

The most common complaints were the same as those experienced by patients receiving the much larger doses of isotretinoin used for the treatment of severe acne and skin cancer (5,6). The high incidence of xerosis and cheilitis was similar to that reported by Strauss et al (7) and was present in 70% of our subjects. However, with the use of lubricants these were not evident on physical examination in half of those affected.

Menstrual changes and headaches were more common than was previously observed. All five women volunteers experienced abnormal menses, as compared to the 15% previously reported (6). Four subjects reported less frequent and/or lighter menses, and two of these patients also reported new midcycle spotting. The fifth subject noted hypermenorrhea and postcoital bleeding. Mild headaches were noted by 70% of the subjects, which is considerably higher than reported in other studies (5,6). However, three subjects attributed these to other causes. Musculoskeletal symptoms were less frequent and were seen in three patients.

Photosensitive eruptions including sunburn were reported by 30% of the patients. Three subjects (30%) had myalgias or arthralgias, prompting one of them to withdraw from the study. Three patients also described dry or burning eye discomfort. Mild epistaxis and palmar-plantar peeling were both reported by two subjects.

Other changes described by one person each were fatigue, brittle hair, abdominal pain, and ear pain. One subject experienced nausea, metallic dysgeusia, increased appetite, decreased alcohol tolerance, mouth sores, swelling and bleeding of the gums, increased irritability, xerosis, cheilitis, myalgias, and headaches. This patient discontinued the isotretinoin.

Laboratory changes were limited to a minor elevation of triglycerides to 319 mg/dl (normal, 50-200) in one in-

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TABLE 1.—Adverse reactions and toxicity levels of normal volunteers receiving oral isotretinoin*

Reaction	Volunteer No.—†									
	1‡	2‡	3	4	5	6	7	8	9	10
Xerosis	I	II	I	II	I			I	I	
Cheilitis	II	III			I	II	I	I		II
Headaches		II		I	I	III	I		I	I
Menstrual changes	II	II	II	II	II					
Musculoskeletal pain	III	III							II	
Sensitivity to sunlight	I	I								
Eye discomfort			I	I			I	I		
Epistaxis				I				I		
Palmar-plantar peeling	I	I								

*Level I toxicity includes dry skin and lips controlled by emollients, increased sunburn susceptibility, mild conjunctivitis controlled with artificial tears, ⩽ 2 nosebleeds/wk, mild palmar-plantar peeling controlled with emollients, and 1-2 mild headaches/wk. Level II toxicity includes dry skin and lips partially controlled with emollients, > 2 mild headaches/wk, hypomenorrhea, eye discomfort incompletely controlled by artificial tears, mild musculoskeletal pain, and palmar-plantar peeling partially controlled with emollients. Level III toxicity includes poorly controlled dry skin and lips, musculoskeletal pain which requires analgesic use, and moderate headaches poorly controlled with analgesics.

†Nos. 1-5 were women and 6-10 were men.

‡Discontinued study medication.

dividual on one occasion.

Although all subjects were aware of toxicity at some point during the 9-month trial, most felt it was not particularly troublesome and all adverse reactions disappeared quickly on discontinuation of the medication. Decreased menses and improvement of acne were frequently commented on as beneficial effects.

Because this investigation was primarily a pharmacokinetic study, there was no control group. The unexpectedly high incidence of side effects prompted this report, although we may have overestimated the frequency of adverse reactions. It is clear from previous experience that there is a significant incidence of reported side effects with placebo therapy. Also, these patients were questioned thoroughly and frequently, and even symptoms which may have been attributable to other causes were included as toxic effects. Finally, the sunny, dry climate in Tucson may have contributed to the xerosis and cheilitis which were experienced by the majority of our subjects.

The usefulness of isotretinoin is limited by the frequency and severity of adverse reactions. Marked toxicity can be tolerated when the disease being treated is severe, such as a malignancy, or when therapy spans a short period, as in the treatment of acne. However, the frequency of adverse reactions to isotretinoin, even at the low doses used in this study, may limit its role in the treatment of minor dermatologic disorders or as a cancer chemopreventive agent in otherwise healthy people.

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Treatment of Advanced Resistant Hodgkin's Disease With Lomustine, Etoposide, and Prednimustine[1]

Francisco Cervantes,* Juan-Carlos Reverter, Emilio Montserrat, and Ciril Rozman[2]

Fifteen patients with Hodgkin's disease resistant to the chemotherapy combinations of cyclophosphamide, vinblastine, procarbazine and prednisone and doxorubicin, bleomycin, vinblastine, and dacarbazine were treated with lomustine, etoposide, and prednimustine. Four of them achieved complete remission and two achieved partial remission (overall response rate, 40%). The median duration of response was 5.5 months, with two complete responders relapsing at 4 and 17 months and the other two remaining disease-free at 7 and 18 months, whereas disease progression was observed at 2.5 and 6 months in the partial responders. Extrahematological toxicity was scarce. Severe myelosuppression was observed in only three patients. These results indicate that lomustine, etoposide, and prednimustine can play a role in the treatment of advanced resistant Hodgkin's disease. [Cancer Treat Rep 70:665–667, 1986]

Most patients with Hodgkin's disease (HD) achieve complete remission (CR) after treatment with either mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) [or cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP)] or doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (1). While relapses occurring beyond 1 year can be successfully retreated with the same original regimen (2), relapses within the first year are often rescued by crossing the original combination chemotherapy, ie, from MOPP to ABVD and conversely (3). However, the optimal therapy of HD resistant to such first-line chemotherapy schemes remains an unresolved question. Recently, Santoro et al (4) reported encouraging results with the CEP (lomustine, etoposide, and prednimustine) regimen in such patients. This combination has not yet been tested in other series.

PATIENTS AND METHODS

Patients

Between May 1983 and December 1985, 15 patients with advanced recurrent HD resistant to CVPP and ABVD were entered in the study. All patients were evaluable. Their main characteristics are shown in table 1. Thirteen of the 15 patients had nodular sclerosis HD, and the remaining two had mixed cellularity HD. In all patients the Karnofsky performance status was $\geq$ 60% at the start of CEP treatment.

Treatment Schedule

The CVPP regimen was the first-choice treatment. When CR was not achieved after six CVPP courses or when it lasted for < 1 year, the patients were given the ABVD regimen. Before ABVD, four of the 15 patients had received other chemotherapy combinations (table 1). When a relapse occurred beyond 1 year of CVPP-induced CR, the patients were re-treated with CVPP; they were then given ABVD if CR was not achieved. The CEP regimen consisted of every-4-week courses of lomustine (80 mg/m^2 orally on Day 1), etoposide (100 mg/m^2 orally on Days 1-5), and prednimustine (60 mg/m^2 orally on Days 1-5). A minimum of three such courses were administered before a failure was considered. Thirteen patients received six CEP cycles. Those patients achieving CR or partial remission (PR) at completion of six cycles were given six additional courses as consolidation therapy and treatment was discontinued.

Criteria of Response

Therapeutic response was evaluated as follows. CR was defined as the disappearance of all signs and symp-

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toms of disease as determined by physical examination, radiographic films, scans, bone marrow and liver biopsies (if previously involved), and blood biochemical studies, for ⩾ 3 months. PR was defined as the disappearance of constitutional symptoms and a reduction > 50% in the product of the longest perpendicular diameters of all sites of measurable disease. Failure was defined as persistence of constitutional symptoms and/or tumor regression < 50%.

RESULTS

Thirteen patients received six chemotherapy courses before evaluation, one died from disease progression after five cycles, and the remaining one refused further treatment after three CEP courses failed in controlling disease progression. Four patients achieved CR and two achieved PR, for an overall favorable response rate of 40%. The four complete responders required four, two, four, and three courses, respectively, to achieve CR, whereas PR was observed only at completion of the six courses in both partial responders.

At this writing, seven of the patients have died, including one of the six responders and six of the nine nonresponders. The median duration of follow-up for all patients is 12 months. Two complete responders relapsed at 4 and 17 months of achieving CR. The other two patients remain disease-free at 7 and 18 months of remission. Both partial responders showed disease progression at 2.5 and 6 months after achieving PR. Overall, the median duration time of the favorable responses to CEP treatment was 5.5 months.

Toxic effects of the CEP regimen were scarce. Only four patients had moderate nausea and vomiting within the 24 hours after drug administration. Moderate alopecia was induced in two patients. One patient developed skin lesions histologically corresponding to lymphocytic angeitis. From a total number of 86 courses administered initially, only three instances of severe myelosuppression were observed, whereas moderate leukopenia and/or thrombocytopenia were registered in another three patients.

DISCUSSION

HD is currently regarded as the malignant hemo-

TABLE 1.—Characteristics of patients with advanced HD treated with CEP

Patient No.	Age (yrs)/sex	Initial stage	Initial treatment	Initial response*	Disease-free interval (mos)	Subsequent treatment†	Subsequent response*	Disease-free interval (mos)	Sites of disease at start of CEP
1	45/M	IIIB	CVPP	CR	12	ABVD	CR	6	Liver
2	14/F	IVB	CVPP	CR	12	ABVD	F	—	Bone marrow
3	38/M	IIIB	CVPP	PR	4	CVB	F	—	Bone involvement
						ABVD	F		
						B-DOPA	F		
4	11/F	IVB	CVPP	PR	—	ABVD	PR	—	Lymph nodes
5	12/M	IIA	CVPP‡	F	—	ABVD	CR	5	Lymph nodes
6	20/F	III_2A	CVPP‡	CR	16	CVPP	CR	33	Bone involvement
						ABVD	F	—	
7	21/F	IIIB	CVPP	CR	18	ABVD	PR	—	Lymph nodes
8	23/M	IVB	CVPP	PR	7	ABVD	PR	—	Lymph nodes
9	20/M	IVB	CVPP	PR	—	ABVD	F	—	Bone involvement
						B-CAVe	F	—	
10	21/M	IVB	CVPP	PR	—	CVB	PR	—	Lymph nodes
						ABVD	CR	13	
11	18/M	III_2B	CVPP	CR	12	ABVD	CR	6	Pleura
12	25/F	IIIB	CVPP	CR	10	CVB	F	—	Lung
						ABVD	CR	17	
13	43/M	IIIB	CVPP	CR	8	ABVD	F	—	Lung
14	19/F	IVB	CVPP	CR	7	ABVD	PR	—	Lymph nodes
15	41/M	IIIB	CVPP	F	—	ABVD	F	—	Lung

*F = failure.

†CVB = lomustine, vinblastine, and bleomycin; B-DOPA = bleomycin, dacarbazine, vincristine, prednisone, and doxorubicin; and B-CAVe = bleomycin, lomustine, doxorubicin, and vinblastine.

‡Plus radiation therapy.

pathy with the highest potential of curability. Thus, 80% of patients with advanced HD achieve CR with MOPP and 68% of them remain disease-free beyond 10 years (1). Moreover, MOPP therapy can often induce a new CR in those patients with a relapse occurring beyond 1 year (2). On the other hand, good results can be obtained with the ABVD combination in patients initially failing MOPP or relapsing within the 1st year following CR (3). Therefore, the MOPP and ABVD regimens are considered as the first-line combination chemotherapy schemes in HD (1). There remains, however, a minority of patients with advanced HD resistant to the above-mentioned regimens either initially or at relapse. The optimal treatment of such patients is not yet well-defined.

In a recent publication, Santoro et al (4) have reported a favorable response rate of 60% in 28 patients with advanced resistant HD treated with the CEP combination. The results here reported confirm in part the experience of these investigators, since the favorable response rate observed in the present series was 40%. On the other hand, the median duration of the good responses was shorter than the 17 months registered by the Milan group. Finally, the moderate toxicity and easy administration on a completely outpatient basis must be included among the advantages of this combination chemotherapy.

In conclusion, the CEP regimen is of value in the treatment of a relatively high proportion of patients with advanced resistant HD and is moderately toxic. Its use in combination with other non-cross-resistant chemotherapy regimens merits investigation.

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Weekly Mitoxantrone Therapy for Refractory Multiple Myeloma: A Southeastern Cancer Study Group Trial[1,2]

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Mitoxantrone is a new agent with activity in breast cancer (1), lymphoma (2), and acute leukemia (3). The Southeastern Cancer Study Group has conducted a phase II trial in refractory multiple myeloma (MM) using a weekly schedule of mitoxantrone.

Patients were eligible if they had confirmed diagnosis of MM refractory to standard chemotherapy; measurable protein abnormality and/or tumor mass; platelet count of at least 50,000/mm^3 and granulocyte count of at least 2000/mm^3; no previous doxorubicin in excess of an accumulated dose of 400 mg/m^2; and no past history of congestive heart failure, ischemic heart disease, or cardiac arrhythmias. Written informed consent was required.

Mitoxantrone (5 mg/m^2 iv in a 30-minute infusion) was given at weekly intervals unless toxicity or disease progression was noted. Toxicity was graded according to standard criteria (4).

Thirty-five adults were entered in this study, of whom three were ineligible and four had inadequate data. Three other patients were evaluable for toxicity only and three were evaluable for survival only. Except for five patients who had had one prior regimen, the others had received two to four prior drug regimens. All patients had received alkylating agents but only two had received prior doxorubicin. Of 22 patients evaluable for response, only one (4.5%) achieved a fair response (a 25% decrease in the M component), which lasted 16 weeks. Toxicity is shown in table 1; myelosuppression was the major toxic effect. Nausea and vomiting were not dose-limiting.

In our patients with refractory MM, hematologic toxicity from mitoxantrone was severe and the 4.5% response rate is disappointing. It should be noted, however, that in malignant lymphomas there is a suggestion that a larger dose every 3 weeks is more effective than the weekly dose schedule (2). Whether better results could be achieved in MM with a different dose schedule or by using this agent earlier in the course of the disease remains to be determined.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Median age in yrs (range): 60 (34-76)	
Karnofsky performance status (%)	
40-60	7
70-90	19
100	2
Sex	
Male	16
Female	12
Race	
White	22
Nonwhite	6
Cell mass	
High	12
Intermediate	11
Low	5
Immunoglobulin type (N = 18)	
IgG	13
IgA	4
IgM	1
Toxic effect (N = 25)	
Granulocytopenia (< 1000 cells/μl)	17
Thrombocytopenia (< 25,000 cells/μl)	1
Drug death (infection)	1
Nausea and vomiting	6
Atrial fibrillation	1

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Phase II Evaluation of Diaziquone in Recurrent Head and Neck Cancer[1,2]

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There exists a subset of patients with recurrent and metastatic squamous carcinoma of the head and neck who cannot receive cisplatin-containing combinations or methotrexate. Additional active agents require identification. A phase II study of diaziquone (AZQ) (1-4)[4] was performed at Wayne State University.

PATIENTS AND METHODS

Twenty-five patients were entered in the study from two Wayne State University-affiliated hospitals, Harper-Grace Hospital, Detroit, MI, and Veterans Administration Hospital, Allen Park, MI. Eligibility criteria included histologic confirmation of squamous carcinoma of the head and neck; measurable disease; pretreatment wbc count $\geq 4000 \times 10^3/mm^3$ and platelet count $\geq 100 \times 10^3/mm^3$; serum creatinine < 2.0 and bilirubin < 2.0 mg; no chemotherapy and/or radiation therapy within 4 weeks prior to receiving AZQ (6 weeks for mitomycin or nitrosoureas); projected survival of at least 6 weeks; Karnofsky performance status of 30%-40%; and informed consent.

Stratification for previous exposure to chemotherapy and irradiation as good and poor risk was performed. Initial good-risk dose was 15 mg/m^2 iv every week × 4 followed by a 2-week rest. Poor-risk dose was 12.5 mg/m^2 iv every week × 4 followed by a 2-week rest. Dose adjustments were made for toxicity. Dose escalation was allowed. An adequate trial of AZQ was four doses provided cytotoxic activity was seen. Standard response criteria were used. Patient characteristics are shown in table 1.

RESULTS

Of the 25 patients entered, 20 are fully evaluable. One patient refused chemotherapy, one was ineligible because of a change in histologic diagnosis, and three died before four doses of drug could be administered. No deaths were treatment-related. One patient on the poor-risk arm experienced a partial response documented by chest x-ray. This partial response lasted 11 weeks. The toxic effects on the good-risk arm included moderate leukopenia (one patient) and moderate thrombocytopenia (two). Poor-risk patients developed three episodes of moderate leukopenia, one episode of severe leukopenia, and three episodes of moderate thrombocytopenia. Anemia occurred in the poor-risk patients from mild to severe (three mild, one moderate, and one severe), with moderate and severe cases requiring transfusion.

DISCUSSION

Patients who have had previous treatment with chemotherapy and irradiation usually have poor results with subsequent treatment. This was apparent in this group of heavily pretreated patients given AZQ. A response rate of 5% (one response among 20 patients) to AZQ is certainly not an indication of activity. We conclude that AZQ has no significant activity in patients with head and neck cancer who have failed prior therapy.

TABLE 1.—Patient characteristics[*]

Characteristic	Good-risk	Poor-risk
Entered	5	20
Eligible	4	20
Evaluable	3	17
Early death	1	2
Sex		
Male	1	15
Female	4	5
Median age (yrs)	71	58
Median Karnofsky performance status (%)	70	80
Previous chemotherapy (%)	0	80
Previous irradiation (%)	60	100

[*] Unless otherwise specified, values = No. of patients.

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Phase II Study of Spirogermanium in Advanced (Extensive) Non-Small Cell Lung Cancer[1,2]

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Spirogermanium is a new azaspiran compound with cytotoxic properties. Its mode of action appears to be through interference with protein synthesis (1). When used alone, it has demonstrated antitumor activity against ovarian, breast, and prostate cancers and lymphomas (2,3). A phase I trial at M. D. Anderson Hospital suggested a dose of 100–200 mg/m^2/day × 5 by 1-hour iv infusion or 200 mg/m^2/day × 5 by continuous 24-hour iv infusion every 3 weeks (4). The present study reports the results of a phase II trial of spirogermanium in advanced non-small cell lung cancer.

Spirogermanium was given at doses of 100 mg/m^2/day × 5 in 250 ml of normal saline by 1-hour iv infusion every other week to 20 patients with histologically documented extensive non-small cell lung cancer with measurable disease. A complete history and physical examination, cbc, urinalysis, SMA-12, chest x-ray, nuclear scans, and computed tomography when indicated were performed before treatment began. The laboratory studies were repeated weekly. Radiologic studies were repeated every 2–4 weeks to evaluate tumor status. Standard criteria of tumor response were used (3). If no toxicity was observed, the dose was escalated to 120 mg/m^2/day × 5 every other week. At least two courses of chemotherapy were required for adequate trial.

Patient characteristics and results are as shown in table 1. Four patients were inevaluable due to inadequate trial. All patients except one had a performance status of 3 or better. Seventeen patients (85%) had had chemotherapy with multiple drugs before entering this study. The disease progressed in all patients. Dose-limiting toxicity was not encountered in 48 evaluable courses. There was no myelosuppression. Neurologic side effects (somnolence, two patients; blurred vision, two; and dizziness and lightheadedness, one each) were mild and transient. Spirogermanium at a dose of 100–120 mg/m^2 daily × 5 given every other week showed no antitumor activity against heavily pretreated advanced non-small cell lung cancer.

TABLE 1.—Patient characteristics and response to administration of spirogermanium in advanced non-small cell lung cancer

Characteristic	No. of patients (%)
Total	20
Sex	
Male	11 (55)
Female	9 (45)
Age in yrs	
Median: 54	
Range: 34–71	
Cell type	
Adenocarcinoma	11 (55)
Squamous cell carcinoma	3 (15)
Poorly differentiated and large cell carcinoma	6 (30)
Performance status	
Ambulatory (0, 1, and 2)	13 (65)
Nonambulatory (3 and 4)*	7 (35)
Previous treatment	
Chemotherapy	10 (50)
Chemotherapy and radiotherapy	7 (35)
Radiotherapy	3 (15)
Results	
Disease progression	16 (80)
Inevaluable	4 (20)

* One patient had performance status of 4.

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Phase II Study of Mitomycin in Small Cell Lung Carcinoma[1]

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MATERIALS AND METHODS

Twenty-four patients with histologically confirmed small cell lung carcinoma (SCLC), measurable disease, Karnofsky performance status > 50%, and adequate bone marrow reserve were studied. All patients had received prior therapy with doxorubicin plus cyclophosphamide-containing regimens. Eleven patients had received doxorubicin, cyclophosphamide, and vincristine; eight had received doxorubicin, cyclophosphamide, and etoposide; and one had received methotrexate, doxorubicin, cyclophosphamide, and lomustine. Seven patients had a subsequent second round of chemotherapy at disease progression, and two had received a third trial of combination chemotherapy prior to initiation of mitomycin. The patient population is described in table 1.

Before initiation of therapy, all patients had a complete history and physical examination, a laboratory evaluation including a cbc and SMA-12, and a posteroanterior and lateral chest x-ray. Radionuclide scans and computerized tomography were performed when indicated. Mitomycin was administered by rapid iv injection at 20 mg/m^2 every 6 weeks. Treatment was withheld if the wbc count was < 3000/mm^3 or if the platelet count was < 100,000/mm^3.

Complete response was defined as the complete disappearance of all measurable disease for > 1 month. Partial response was defined as a > 50% reduction in the sum of the products of the largest perpendicular diameter of measurable disease for > 1 month.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Evaluable	20
Median age in yrs (range): 58.5 (42-73)	
Sex	
Male	15
Female	5
Median Karnofsky performance status (range): 70% (60%-80%)	
No. of prior combination regimens	
1	11
2	7
3	2

RESULTS

There were 24 patients included in this trial. Records from 20 patients were available for review. There were no complete or partial responses. Five patients had stable disease for 3-5 months. Twelve patients had disease progression after one cycle of chemotherapy. One patient with stable disease had a severe necrotizing hypersensitivity reaction to the drug, necessitating cessation of therapy. Median survival was 77.5 days (range, 24-393).

DISCUSSION

Mitomycin was evaluated in previously treated SCLC. In 20 evaluable patients, there were no objective responses. This precludes a 20% level of activity with a 95% confidence. This lack of activity has also been reported for mitomycin as a single agent in a European study (1) and in a combination regimen (2). We conclude that mitomycin at this dose schedule has no activity in previously treated patients with SCLC.

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Phase II Trial of Chemotherapy With Cisplatin and Etoposide in Non-Small Cell Lung Cancer[1]

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Combination chemotherapy with cisplatin (CDDP) and etoposide (VP-16) has been found effective in non-small cell lung cancer (NSCLC) by several investigators (1-3). We report the results of a clinical phase II trial using these drugs.

PATIENTS AND METHODS

Sixteen patients with biopsy-proven inoperable NSCLC (14 advanced and two limited with impaired respiratory function) were admitted in the study (table 1). No patients had been previously treated and all had measurable or evaluable disease.

The therapeutic regimen consisted of CDDP (60 mg/m^2) on Day 1 and VP-16 (120 mg/m^2 iv) on Days 1, 3, and 5, repeated every 4 weeks. Treatment was stopped whenever disease progression was evident or no response was achieved after at least three courses. Median follow-up was 36 weeks. World Health Organization criteria of response and toxicity were used.

RESULTS

All patients were evaluable for response and toxicity. No objective responses were achieved, and seven patients had stable disease and nine had disease progression. The median survival of the whole group was 32 weeks. Chemotherapy toxicity was moderate (table 1).

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	16
Median age in yrs (range): 57 (30-68)	
Sex	
Male/female	15/1
Stage*	
II	2
III	7
IV	7
Histology	
Squamous cell carcinoma	6
Large cell carcinoma	3
Undifferentiated NSCLC	7
Median Karnofsky performance status (range): 80 (60-90)	
Median chemotherapy cycles (range): 3 (1-8)	
Toxic effect	
Hematologic	
Grade I (leukopenia)	2
Grade II (leukopenia)	2
Grade II (anemia)	1
Gastrointestinal	
Grade I	3
Grade II	5
Grade III	8
Renal	0

* International Union Against Cancer criteria.

DISCUSSION

Although the doses and schedule of CDDP plus VP-16 were similar to those described (1-3), we have not obtained any response, whereas the other investigators had reported up to 47% response, mainly partial response. The median survival in our group, however, is equivalent to that reported in those series, probably because patients achieving partial response and those having stable disease usually have similar survival times (4).

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Phase II Evaluation of Procarbazine in Metastatic Breast Cancer: A Southeastern Cancer Study Group Trial[1,2]

John T. Carpenter, Jr,* Marilyn Raney, and Theresa Logan[3]

In 1981, Valdivia et al (1) reported that procarbazine (300 mg/m^2/day for 21 of every 28 days) produced a 35% response rate in patients with metastatic breast carcinoma. The Southeastern Cancer Study Group (SEG) undertook the present study from March 1983 through January 1984 to confirm that report.

Women with biopsy-proven, incurable, metastatic breast carcinoma were eligible if their disease was refractory to standard chemotherapy (cyclophosphamide, doxorubicin, and methotrexate) and to hormonal therapy if their tumors contained estrogen receptors. All patients had previously received two or more regimens of chemotherapy and most had also received hormonal therapy. A measurable lesion, Karnofsky performance status ≥ 50%, written informed consent, and recovery from previous myelosuppressive therapy were required. Procarbazine was prescribed orally at doses of 50 mg the first day, 100 mg the second day, 150 mg the third day, etc, until a dose of 200 mg/m^2 was reached and continued at that dose for the remainder of a 21-day course which was followed by 7 days off treatment. A second similar course was given beginning on the 29th day; if no severe toxicity occurred during the first course, the dose in the second course was incrementally escalated to 250 mg/m^2. An adequate trial was defined as two courses of therapy unless no limiting (severe) toxicity occurred, in which case a third course was given in doses incrementally escalated to 300 mg/m^2. Partial response (PR) was defined as a reduction of at least 50% in the sum of the products of perpendicular diameters of all lesions. Toxic effects were graded according to standard SEG criteria (2).

Of 45 patients entered, one was not eligible and one refused to start treatment. The others are shown in table 1. No patient tolerated the drug well enough to be escalated to the 300-mg/m^2/day level. There was only one PR among 22 adequate trials.

Severe gastrointestinal toxicity occurred in 15 of 43 patients (seven of the 15 had liver metastases) and was the principal reason for early withdrawal from the study; it

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Median age in yrs (range): 59 (36–81)	
Karnofsky performance status (%)	
80–100	16
50–70	26
Not known	1
Dominant site of metastases	
Hepatic and/or pulmonary	30
Bone and/or soft tissue	13
Response to therapy	
PR	1
Stable disease	7
Disease progression	14
Withdrawn early or refused therapy due to severe vomiting (13 patients), or early death due to probable myocardial infarction (1 patient) and confusion and life-threatening cardiomyopathy (1 patient)	15
Insufficient data to determine response	6
Median survival on study in mos (range): 3.7 (0.3–15)	
Toxic effect	
Hematologic	
Granulocytopenia	
1000–2000 cells/μl	5
< 1000 cells/μl	5
Infection with granulocytopenia	4
Drug death (infection with granulocytopenia)	1
Thrombocytopenia	
50,000–130,000 cells/μl	8
< 50,000 cells/μl	9
Hemoglobin (≥ 25% decrease)	1
Hepatic (enzymes ≥ twice normal value)	5
Nausea/vomiting (controlled with antiemetics)	12
Nausea/vomiting (persistent vomiting despite antiemetic use)	15
Neurologic (all grade I or II)	
Confusion/ataxia	10
Peripheral neuropathy	6

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was apparently much more marked than that previously reported (1).

The severe toxicity and lack of response to procarbazine suggest that it is neither tolerable nor effective in breast cancer when used according to this schedule.

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Phase II Trial of *N*-Methylformamide for Advanced Renal Cell Carcinoma[1,2]

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N-Methylformamide (NMF) is an antitumor polar solvent which induces differentiation in human tumor lines (1). Preclinical studies revealed no drug-induced myelosuppression; however, reversible hepatotoxicity, nausea, vomiting, anorexia, and sleeplessness were noted (2). A phase II disease-oriented trial for patients with advanced renal cell carcinoma (RCC) was initiated at Memorial Hospital, Memorial Sloan-Kettering Cancer Center, and forms the basis of this report.

Eighteen patients with bidimensionally measurable, pathologically confirmed RCC received NMF. There were 14 males and four females, with a median age of 55 years (range, 42–70) and a Karnofsky performance status (KPS) of 80% (range, 60%–100%). Time from diagnosis to protocol was 17 months (range, 0.5–90). All patients had complete medical history, physical examination with measurement of palpable lesions by two observers, absolute basophil count, SMA-12, 5′-nucleotidase, GGTP, KPS, chest x-ray, and appropriate diagnostic tests needed to evaluate response [ie, radionuclide scan and computerized tomographic (CT) scan]. Patient entry required adequate hematologic parameters (wbc count $\geq 3000/mm^3$; platelet count $\geq 120{,}000/mm^3$), KPS $\geq 50\%$, bilirubin ≤ 1.5 mg/dl, alkaline phosphatase, SGOT $\leq 1.5 \times$ normal, BUN ≤ 30 mg/dl, creatinine ≤ 2 mg/dl, and informed consent. Prior hormones, immunotherapy, and cytotoxic drugs were discontinued at least 3 weeks prior to NMF. Fourteen patients had had no prior chemotherapy, four had received prior irradiation, five had had immunotherapy (four interferon, one transfer factor), and three had received hormones. Primary indicator lesions were lung (14 patients) and abdominal mass by CT scan (four patients). In addition, five patients as indicated by CT scan had abdominal masses, one had malignant hepatomegaly, and one had sc nodes on physical examination. An adequate trial was one course with toxic effects and/or disease progression. A partial remission was defined as a $\geq 50\%$ decrease in the summed products of perpendicular diameters of all measurable lesions for ≥ 1 month; stable disease was defined as a 25% change in tumor size for 3 months; and disease progression was defined as a 25% increase.

Initially, NMF was given at 1000 mg/m^2 iv $\times$ 5 days every 4 weeks. To assess liver toxicity, most patients had biochemical tests obtained on Days 3–5 of the initial cycle, and every week thereafter. Because of significant hepatic toxic effects (2+–3+), the starting dose was decreased to 800–900 mg/m^2 in five patients. Fifty-five courses were given (median, two courses; range, one to 11); six patients had one course, nine had two to three courses, and three had eight to 11. No responses occurred in 16 adequately treated patients (95% confidence limits, 0%–17%), 13 of whom were not pretreated. Three patients had stable disease for 9, 11, and 13 months, respectively. Two patients were considered inadequately treated, but were evaluable for toxicity. Ten patients had a subsequent NMF dose reduction, nine received 800 mg/m^2, and one received 900 mg/m^2.

The dose-limiting toxic effect was hepatotoxicity, ranging from asymptomatic biochemical changes to liver pain. Liver function test abnormalities were seen by Day 3, with peak elevations by Days 5–7. Compared to baseline/normal (B/N) entry levels, bilirubin increased in nine patients to 1.6 mg/dl $\times$ B/N (median, 1.6; range, 1.1–6.8); SGOT in 17 patients to 3.8 U/L $\times$ B/N (median, 65; range, 28–289); GGTP in 11 patients to 6 U/L $\times$ B/N (median, 229; range, 55–948); 5′-nucleotidase in 13 patients to 2.9 U/L $\times$ B/N (median, 40; range, 18–190); alkaline phosphatase in 11 patients to 1.8 U/L $\times$ B/N (median, 202; range, 121–753); and LDH in nine patients to 1.3 U/L $\times$ B/N (median, 292; range, 250–912). Return to baseline levels in all patients was between Days 14 and 21 of each cycle. Nausea and vomiting were noted in nine patients. No significant myelosuppression occurred; median wbc and platelet count nadirs were $6900/mm^3$ (range, 3800–9500) and $210{,}000/mm^3$ (range, 75,000–383,000), respectively.

The serum phosphorus concentration rapidly decreased by Day 3, with a continued downward trend through Day 5 unless oral or iv replacement was begun. Hypophosphatemia (< 2.5 mg/dl) developed in 13 patients, with median nadir of 2.1 mg/dl (range, 1.5–3.0) on Day 5 (range,

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3–9). No consistent change in serum calcium or albumin levels occurred. Moderately severe muscular aches and pains and "restlessness" often accompanied by insomnia occurred in 11 of 13 patients. Such symptoms have been described with low serum phosphorus levels as have generalized anorexia, malaise, weakness, paresthesias, muscle aches, ataxia, seizures, and coma (3). With oral phosphorus (250 mg three times a day every day) and soporific agents, symptomatic improvement occurred.

Since NMF at this dosage and schedule induced no response among 16 patients (95% confidence limits, 0%–17%), it has no role for advanced RCC.

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Phase II Trial of Esorubicin in Advanced Pancreatic Adenocarcinoma[1,2]

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Esorubicin (4′-deoxydoxorubicin) is an analog of doxorubicin and has greater potency and diminished cardiotoxicity in murine models (1) and activity in human phase I studies (2,3). We studied esorubicin in patients who had advanced, measurable adenocarcinoma of the pancreas.

Eighteen patients, previously untreated with either irradiation or chemotherapy, who had biopsy-proven adenocarcinoma of the pancreas were entered in this study (table 1). The esorubicin dose was 35 mg/m^2 of ideal body weight repeated every 3-4 weeks; 25% and 50% reduction of initial dose was employed for bilirubin between 1.5 and 3.0 mg/dl and for bilirubin > 3.0 mg/dl, respectively. All patients had measurable disease on computed tomography (CT) scan and were treated at our institution. Dose escalation was employed until at least grade 3 hematologic toxicity developed. Standard criteria (from the Southeastern Cancer Study Group) were used to assess response, and information was recorded with the aid of Symphony software (Lotus Development, Cambridge, MA).

Sixteen patients were treated for a minimum of two cycles and are evaluable for both response and toxicity; two patients had disease-related death within the first 3 weeks of entry and are evaluable only for acute toxicity. None of the 16 patients had an objective clinical or radiographic response.

Treatment was well-tolerated. Granulocyte toxicity was dose-limiting, and all patients developed at least grade 3 leukopenia. Doses of 42 mg/m^2 resulted in a mean granulocyte count nadir of 0.88/dl, 35 mg/m^2 resulted in a mean granulocyte count nadir of 1.2/dl, and 27 mg/m^2 resulted in a mean granulocyte count nadir of 2.2/dl. Thrombocytopenia, nausea and vomiting, and alopecia were all mild (grade 2 or less). Two patients developed subclinical cardiac toxicity, manifested as an absolute 15% decrement from baseline of the cardiac ejection fraction (determined by gated radionuclide angiography), and

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Evaluable for response and toxicity	16
Median age in yrs (range): 52 (28-73)	
Mean Karnofsky performance status (range): 76% (50%-90%)	
Sex	
Male	7
Female	9
Previous chemotherapy or radiotherapy	0
Patients receiving 35 mg/m^2 on at least 1 treatment cycle	16
Mean total dose administered in mg/m^2 (range): 114 (44-236)	
Response (compiete or partial)	0
Median survival in mos (range): 4.2 (0.8-10+)	
Toxic effects*	
Hematologic	
Granulocyte count	
Grade 4 (< 500/dl)	8
Grade 3 (1000-500/dl)	8
Platelet count	
Grade 3	2
Grade 2	4
Grade 1	1
Grade 0	9
Acute nausea and vomiting (n = 18)	
Grade 2	2
Grade 1	3
Grade 0	13
Alopecia	
Grade 2	1
Grade 1	3
Grade 0	12
Skin	
Grade 1	3
Grade 0	13

* Most severe grade achieved.

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[2]This study was approved by the City of Hope Institutional Review Board for the Protection of Human Subjects. All patients gave informed consent for participation in this study.

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their treatment was halted. Two patients had drug extravasations and developed chronic, tender erythema at the injection site which resolved without skin grafting or other specific treatment. Three other patients had tender nodules develop at venous access sites without a known extravasation.

We conclude that esorubicin, when used alone and given at maximum tolerated doses in an every 3–4-week bolus schedule, is without activity in patients with adenocarcinoma of the pancreas. Cardiotoxicity may be a problem with this drug dose and schedule (4) and will have to be evaluated in other studies in which prolonged treatment is given. Esorubicin is well-tolerated, and if activity can be demonstrated in other diseases, may be a clinically useful alternative to doxorubicin.

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Phase II Trial of Bisantrene in Patients With Advanced Sarcoma: A Southwest Oncology Group Study[1,2]

John D. Cowan,[3] Edmund Gehan,[4] Saul E. Rivkin,[5] and Stephen E. Jones[6,*]

Bisantrene is a new anthracene compound which, in preclinical screening, showed activity in a number of animal tumor systems (1) and in the human tumor cloning assay (2). A phase I study of bisantrene, using a single-dose every-3-week schedule, demonstrated that its dose-limiting toxic effect was leukopenia (3). Based on these data, the present phase II study was performed to determine the antitumor effect of bisantrene in previously treated patients with advanced sarcoma.

PATIENTS AND METHODS

Eligibility criteria included histologically confirmed metastatic advanced sarcoma in previously treated patients, informed consent, an evaluable lesion, performance status ≤ 3 (Southwest Oncology Group criteria), no significant cardiac disease, prior treatment with ≤ 400 mg/m^2 of doxorubicin, no concomitant antitumor therapy, wbc count > 4000/μl, platelet count > 125,000/μl, serum creatinine ≤ 2 mg/dl, and bilirubin ≤ 2 mg/dl. Patient characteristics are shown in table 1.

Based on a phase I study (3), bisantrene was administered iv at an initial dose of 260 mg/m^2 (208 mg/m^2 in poor-risk patients) over at least 120 minutes in 1000 ml of 5% dextrose in water. Use of a central venous catheter was encouraged because of drug infusion-associated phlebitis. Patients were pretreated with 50 mg of diphenhydramine hydrochloride im and 100 mg of hydrocortisone sodium succinate iv to decrease the risk of anaphylaxis (3). The dose was repeated every 3 weeks if the wbc count was > 3500/μl and if the platelet count was > 125,000/μl. Dose modifications were encouraged and were based on the wbc count and platelet count nadirs. If the wbc count nadir was > 4000/μl and if the platelet count nadir was > 100,000/μl, the dose was increased by 10%. If the wbc count nadir was < 2000/μl and/or the platelet count nadir was < 50,000/μl, the dose was decreased by 20%. Standard objective response criteria were used.

RESULTS

Twenty-one patients were entered in the study, with 20 patients eligible for toxicity and response evaluation. One patient was registered but not treated. Forty-eight cycles of therapy were given, with the major toxic effect limited to neutropenia. The median neutrophil count was 1657/μl (range, 396–5400). There were no life-threatening infections identified. Thrombocytopenia was noted with one course (25,000/μl) and uncomplicated by bleeding. There was one cycle of therapy complicated by reversible hypotension at a dose of 260 mg/m^2 after appropriate premedication with diphenhydramine hydrochloride and hydrocortisone. The hypotension occurred at 2 hours 45 minutes into the infusion with blood pressure decreasing from 152/78 to 104/70. The drop in blood pressure responded to saline challenge. The patient had been previously treated with three cycles of bisantrene without hypotension and subsequently was treated with one additional cycle of therapy at a 20% dose reduction, without recurrence of hypotension. Other nonhematologic toxic effects were mild, with nausea and vomiting noted in four cycles (8%). Drug treatment-associated phlebitis occurred only in patients receiving bisantrene by peripheral vein. There was no cardiac, renal, or hepatic toxicity. There were no drug-related deaths.

There were no responses. Three patients had stable disease for 8, 12, and 22 weeks. The median survival of all patients was 10 weeks (range, 4–100+).

DISCUSSION

Bisantrene was well-tolerated in this heavily pretreated cohort of patients without significant toxic effects.

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TABLE 1.—Patient and treatment data

Characteristic	No. of patients
Median age in yrs (range): 46 (24–66)	
Median performance status (range): 2 (0–3)	
Good-risk/poor-risk	15/6
Prior therapy	
Chemotherapy	19
Doxorubicin	18
Median No. of drugs (range): 2 (0–4)	
Radiation therapy	9
Histologic type	
Soft tissue sarcoma	17
Non-soft tissue sarcoma	4
Site of indicator lesions	
Lung	13
Soft tissue	5
Intra-abdominal	5
Liver	2
Measurement of indicator lesions	
Chest x-ray	13
Computed tomography	8
Physical examination	5
Nuclear scan	1

There were no cumulative toxic effects noted. Clinical activity of bisantrene was not identified in these heavily pretreated patients using a 260-mg/m^2 every-3-week schedule. There is a reported steep dose-response curve for the anthracycline, doxorubicin, in soft tissue sarcoma (4). A similar steep dose-response curve may be present for bisantrene. Future study of bisantrene in sarcoma should only be considered at a higher dose and in patients not previously treated with doxorubicin.

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Cutaneous Necrosis After Intra-arterial Treatment With Cisplatin

Local tissue toxicity caused by extravasation accounts for approximately 2%–5% of all adverse effects from antineoplastic drugs (1). This complication is very rare with cisplatin (CDDP). Recently, we observed one case of local necrosis secondary to extravasation of CDDP in a patient with a fibrosarcoma of the right forearm.

CASE REPORT

A 48-year-old female presented in 1959 with a slow-growing painful tumor mass of the right wrist. Local excision was performed at another hospital and the pathological report revealed low-grade fibrosarcoma. The tumor mass reappeared following local excision on three occasions between 1980 and 1985. The pathology report always confirmed the initial diagnosis. After the second excision, involvement of the median and ulnar nerves was observed and radiotherapy was given to the affected area. During the last excision in November 1984, tumor invasion of the ulnar nerve and artery was noticed. The patient was then referred to our service for intra-arterial chemotherapy. Initial physical examination revealed a hard, fixed, non-tender nodule in the ulnar side of the wrist measuring 2.5 × 3.7 cm which produced marked functional impairment. She was treated with intra-arterial CDDP, 40 mg diluted in 40 ml of physiological solution by transfemoral catheterization using a Judkins catheter with a tip in the right humeral artery. The same procedure and dosage of CDDP was repeated twice on the following days for a total CDDP dosage of 120 mg without any complications. The patient was readmitted 28 days later for a second cycle of treatment. At this time, physical examination indicated a decrease in the nodule's size and consistency with improvement of the movement of the wrist. Because of periarterial fibrosis, the second CDDP treatment had to be given directly into the right humeral artery at the level of the elbow using an Abbocath gauze 20. Three days later, CDDP was given 4 cm above the anterior puncture site and local extravasation of approximately 1.5 ml of the CDDP solution took place. The injection was stopped immediately and local aspiration was done. Corticosteroids were injected sc in and around the extravasation site. On the next day, edema and erythema were noted in the affected area. After a few days, a vesicular eruption forming a bleb appeared followed by a 6-cm necrotic plaque which was treated with topical corticosteroid and antibiotic treatment.

On her next admission for the third cycle of treatment, the patient presented with a hard 3-cm black scar in the right forearm with massive necrosis on the puncture site (fig 1).

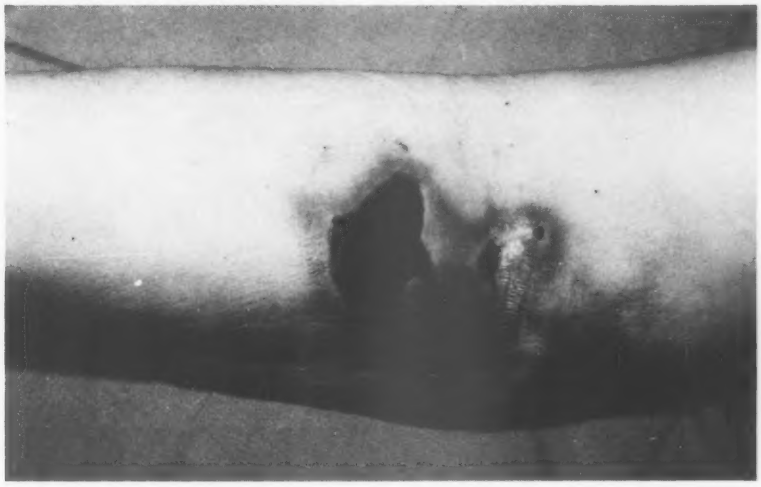

FIGURE 1.—Massive necrosis in the right forearm after intra-arterial CDDP.

DISCUSSION

Isolated hyperthermic perfusion with CDDP (either alone or in combination with other cytostatic agents) has been utilized in the local treatment of limb tumors (2). Complications such as local nerve damage have been reported in relation to the application of heat > 40°C, particularly in the lower limb and foot (3).

Local extravasation caused by many chemotherapeutic agents and solutions that are hypertonic, highly acidic, or alkaline may cause serious damage. To our knowledge [although CDDP in an aqueous solution has an acidic pH (3.5–5.5) (4)], local cutaneous necrosis secondary to this drug administered iv has been described only once prior to this report (5). We believe that this rare adverse effect is so uncommon, perhaps because iv CDDP is usually administered in a large diluted volume and infused over several hours. This makes it unlikely that a large quantity of CDDP might be extravasated without notice.

The pH of our CDDP solution was 5.5. Therefore, we consider that the lesion reported here can very well be attributed to direct CDDP cytotoxicity.

Of our experiences using intra-arterial CDDP at the University Clinic of Navarra (which has > 200 patients), this was the first local cutaneous necrosis observed.

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Lomustine, Bleomycin, and Cisplatin in Patients With Metastatic Malignant Melanoma[1]

Malignant melanoma remains a disease for which long-term effective chemotherapy is unavailable. In 1980, Newburger and Young (1) observed that alternations of cell kinetics in melanotic nodules seen 48 hours after semustine persisted for several days in responders. This led them to postulate that the 48-hour point might be the logical time to give a second drug to inhibit tumor cell repair. In 1980, Nathanson et al (2) reported a 57% response rate in metastatic melanoma with a regimen consisting of vinblastine, bleomycin, and cisplatin (VBD).

We evaluated a combination chemotherapy regimen substituting lomustine (80 mg/m^2 on Day 1) for vinblastine followed 48 hours later by bleomycin (15 units/m^2/24 hours given in 500 ml of 5% glucose in water daily from Days 3 to 7 as a continuous infusion) followed by cisplatin (40 mg/m^2 on Day 8 iv in 100 ml of normal saline over 30 minutes after overnight hydration). Cycles of therapy were repeated every 42 days. In the absence of toxicity and response, the dose of lomustine was increased to 100 mg/m^2. In the absence of renal toxicity and response, the dose of cisplatin was increased to 50 mg/m^2.

During the early phase of the study, we noted six patients relapsing just prior to the initiation or shortly after completion of the second cycle of chemotherapy. Because of this early disease progression, we treated five patients with additional doses of cisplatin on Day 21 of each cycle. After the third cycle, maintenance therapy consisted of lomustine, 40 mg/m^2 on Day 1, and cisplatin, 40 mg/m^2 on Days 3 and 21 of each 6-week cycle.

Cbcs and biochemical profiles were performed at least every 3 weeks. If the wbc count was < 4000/μl or the platelet count was < 100,000/μl, therapy was delayed 1 week or until hematological recovery (four patients).

A total of 25 evaluable patients entered the study. There were 15 women and ten men, with a median age of 43 years (range, 22–82). The performance status (Zubrod) was 0 in three patients, 1 in eight, 2 in four, 3 in one, and 4 in nine. Eight patients had previously been treated with chemotherapy (dacarbazine alone; bleomycin, carmustine, vincristine plus dacarbazine; dacarbazine plus cyclophosphamide; lomustine plus vincristine; dacarbazine, vincristine, lomustine plus dactinomycin). Involved areas were: skin and node alone, four patients; skin and node plus viscera, 12; hepatic, nine; pulmonary, six; and brain, four. Four patients had disease confined to subcutaneous and nodal areas only. Patients achieving at least a 50% regression in the areas of disease lasting ≥ 4 weeks without disease progression or new lesions elsewhere were classified as partial responders.

Twelve patients (48%) achieved partial response. The

[1]Supported in part by Public Health Service grant CA-15936 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by the Chemotherapy Foundation, Inc, New York, NY.

response rate was higher among women (ten of 15 women vs two of ten men), irrespective of menopausal status (five of seven pre- vs five of eight post-menopausal) or prior exposure to chemotherapy (three of 12 responders and five of 13 nonresponders). The response duration ranged from 4 to 82+ weeks, with a mean and median response duration of 26 and 10 weeks, respectively. The mean and median survivals for responders were 41 and 32 weeks, respectively; those of the nonresponders were 16 and 14 weeks, respectively. Responses were seen mainly in women with nodal, cutaneous, and subcutaneous involvement; eight (all women) of 16 patients (ten women and six men) with this category of involvement responded and three of four patients whose disease was confined only in the cutaneous and nodal areas responded. In addition, two (both women) of nine patients (five women and four men) with hepatic involvement and two (one woman and one man) of six patients (two women and four men) with pulmonary involvement responded. Four patients survived > 1 year. They included two with extensive hepatic involvement, another with retroperitoneal disease, and the fourth with cerebral metastasis.

Of five patients receiving cisplatin every 3 weeks, two had response durations of 6 and 12 weeks, respectively, but due to the small number of patients we were unable to assess the question of whether shortening the interval between courses of cisplatin can improve response rate or duration. Similarly, the merit of nitrosourea employed in a chronologic fashion cannot be assessed properly without a randomized study with an arm administering the nitrosourea concurrent with the two other drugs.

Nineteen of the 25 patients developed a wbc count < 4000/μl or a platelet count < 100,000/μl. Three patients died of septicemia during episodes of chemotherapy-induced leukopenia; all of them had a performance status of 4. This regimen should be attenuated for patients with poor performance status. There were no other serious complications.

Our observation is significant in that following the initiation of our trial, several reports appeared which failed to confirm the high response rate of VBD initially reported by Nathanson et al (3-5).

Albeit limitations discussed above, high responses seen in a subcategory of patients are encouraging and this regimen may serve as a basis for future combinations.

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Severe Hyponatremia Following Simultaneous Administration of Aminoglutethimide and Diuretics

Aminoglutethimide has been found to be active in advanced breast cancer, especially in postmenopausal women (1), and has gained increasing use in clinical conditions. It is known to decrease the production of glucocorticoids as well as aldosterone by inhibition of the conversion of cholesterol to pregnenolone (2). It has also been found that hydrocortisone alone is sufficient as replacement therapy (3). We therefore find it of interest to report a case of pronounced hyponatremia developing in a patient simultaneously treated with a diuretic.

A 68-year-old woman with advanced breast cancer was treated with aminoglutethimide (250 mg four times a day) and hydrocortisone (20 mg three times a day). The patient had been treated with bendroflumethiazide (2.5 mg) and potassium chloride (578 mg), four tablets a day for several years, for mild hypertension and cardiac incompensation.

After 10 months of treatment, the patient was admitted to our hospital because of increasing weakness. Serum sodium was 100 mmols/L (range, 136-146). Serum creatinine, potassium, calcium, and total CO_2 were within normal levels. Urine sodium was found to be < 20 mmols/L/day during 4 days. Aldosterone was not measured.

After discontinuation of aminoglutethimide plus hydrocortisone and the diuretic, serum sodium rose slowly to normal values without sodium supply. Resuming the treatment with aminoglutethimide plus hydrocortisone alone, we found no significant alterations of electrolyte levels over a period of 3 months. In contrast, addition of the diuretic medication caused serum sodium to fall slowly from 140 to 124 mmols/L within 4 weeks. Subsequently, the serum sodium concentration was normalized after the administration of fludrocortisone (0.1

mg daily).

To our knowledge, this enhanced side effect has not been reported before. We wish to draw attention to the apparently synergistic effect between the lack of mineralocorticoid and concomitant treatment with a diuretic.

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Apparent Myocardial Ischemia Associated With Vinblastine Administration

Several reports indicate that myocardial ischemia and infarction occur in association with the administration of the vinca alkaloids (1-4). The mechanism of this toxicity is not understood. A recent report by Yancey and Talpaz (4) describes reversible ECG changes occurring during vindesine administration, suggesting a pattern similar to Prinzmetal's angina. They therefore suggested the use of calcium channel blockers in the clinical setting of angina with vinca alkaloid administration. We would like to describe a patient who experienced myocardial ischemia with ECG changes during vinblastine administration despite concurrent use of a calcium channel blocker.

CASE REPORT

A 62-year-old woman with squamous cell carcinoma of the lung was to be treated with vinblastine (4 mg/m^2 on Days 1 and 2) and cisplatin (20 mg/m^2 on Days 1, 2, and 3). She had a previous history of an inferior wall myocardial infarction 1½ years earlier, mild chronic obstructive pulmonary disease, and diet-controlled diabetes mellitus. She was without chest pain at home, maintained on Isordil (40 mg every 8 hrs) and verapamil (80 mg every 8 hrs). She presented with weight loss and a new cough. An endobronchial lesion was found obstructing the left upper lobe bronchus. A biopsy performed on March 15, 1985, showed squamous cell carcinoma. Chemotherapy was begun as described above. Eight hours after the first dose was administered, she experienced substernal chest pain and slight nausea without vomiting. ECG showed an anterolateral subendocardial myocardial infarction. Sublingual nitroglycerin and an increase in Isordil to 120 mg every 8 hours controlled pain. ECG changes persisted, and cardiac enzymes were elevated. Chemotherapy was discontinued after Day 1. The patient was observed on ambulatory cardiac monitoring for 2 weeks, during which time she was active and pain-free. Formal stress testing was not done due to patient refusal. However, 24-hour Holter monitor was unremarkable. Chemotherapy was reinstituted with a 33% reduction in the cisplatin dose to avoid excessive nausea. Again, she experienced chest pain and one episode of vomiting, with pseudonormalization of T waves anteriorly. Sublingual nitroglycerin controlled pain. This time the ECG changes reversed, and cardiac enzymes were within normal limits. Chemotherapy was continued on Days 2 and 3 with cisplatin alone and was well tolerated. The patient has subsequently received irradiation to the hilum and oral methotrexate with no recurrence of angina; as of October 10, 1985, the patient is stable, with cough being her only symptom.

DISCUSSION

The vinca alkaloids are commonly used antineoplastic agents with well-known side effects such as neuropathy for vincristine, and myelosuppression for vinblastine and vindesine. Myocardial damage with these agents has rarely been reported; our current case constitutes another report. Possible mechanisms for this complication include a direct effect on the platelets, or blood clotting mechanism resulting in coronary artery thrombosis. Mandel and co-workers (1) tested this hypothesis by studying the in vitro effect of vincristine on blood specimens obtained from a patient who had a myocardial infarction when treated with vincristine. They found no effect on the parameters tested, including platelet aggregation, fibrinogen, factor III, fibrin stabilization factors, clotting time, euglobulin lysis time, clot retraction, prothrombin time, recalcification time, kaolin-cefalin clotting time, and thromboplastin generation time. Yancey and Talpaz (4) tried to prevent ischemia in one patient by pretreating with aspirin and sulfinpyrazone. However, the patient did have angina on the second treatment with vindesine.

A second hypothesis used to explain the ischemia is the occurrence of coronary artery spasm in response to the vinca alkaloids. No animal models have been studied. Our case illustrates the inability to prevent ischemia with ECG changes with concurrent use of standard-dose verapamil during vinblastine treatment.

It is also possible that the drugs have a direct effect on the myocardial cells causing local anoxia. Finally, the

ischemia may be multifactorial with an element of coronary artery spasm, in combination with an increased sensitivity of the myocardium to hypoxia.

Although our patient tolerated completion of therapy with cisplatin without further incidents, one cannot completely exclude this or factors associated with emesis as playing a role. In fact, there have been several recent reports of cardiac ischemia during the use of other chemotherapeutic agents, such as 5-FU (5). A suspected mechanism for this has also been coronary artery spasm.

The problem of chest pain during chemotherapy treatments may be more frequent than previously reported. Many of these cases may have been attributed to causes other than the drug treatment itself. That anginal syndromes can be a toxicity of the specific drug or drug class is suggested by its documentation with all three clinically used vinca alkaloids. More investigation into the cause of this occurrence is warranted.

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Intractable Pain in Patients With Advanced Head and Neck Tumors: A Possible Role of Local Infection

Research in pain control has recently focused on adjuvant drugs (steroids, muscle relaxants, psychotropics) (1,2) that might enhance the analgesic effect or decrease the toxicity of narcotics. We would like to emphasize that another group of commonly used agents, antibiotics, should be considered as useful adjuvant analgesics in certain situations. Severe chronic pain is commonly present in patients with locally advanced head and neck tumors. It is usually treated with narcotic analgesics. Neurosurgical or anesthesiologic procedures are often precluded because of the location of the pain. In many cases, the patient needs to be admitted for pain control or because of cachexia caused by pain associated with swallowing (3).

We report seven patients who had a sudden increase in the intensity of pain, leading to hospital admission in six of the patients. In all patients, antibiotic treatment produced a marked and rapid improvement in pain control, making discharge possible in four of the six admitted patients.

The mean age of the patients was 59 years (range, 29-74); three patients (Nos. 1, 3, and 6) were female. All patients had locally recurrent epidermoid carcinomas; in six patients the primary tumor was in the tongue and in one (No. 6) it was in the floor of the mouth. All of the patients had large ulcerated tumors (table 1). All of the patients reported good pain control with oral narcotics until an average of 3 days before consultation, when pain became severe and was associated with a decrease in solid and liquid intake because of dysphagia. Physical examination showed large tumor masses with ulceration and necrosis, as well as induration, swelling, and erythema in the surrounding tissues. However, all of these findings were not new; only three patients showed minor changes in the aspect of their lesions (Patients 1 and 2 had new soft painful lymph nodes in the neck and Patients 2 and 7 had an increase in skin erythema). Table 1 summarizes the rest of the findings, as well as analgesic and antibiotic treatments.

All of the patients, except Patient 1, were admitted to the hospital, and four of the six patients were discharged home after antibiotic treatment (Patient 4 remained in the hospital for a gastrostomy and Patient 6 for enteral feeding; both patients died in the hospital in good pain control). Both patients who had an increase in wbc counts (Nos. 5 and 7) had a normalization of their counts after antibiotics, and the three patients that showed recent changes in their lesions showed marked improvement after antibiotic therapy. Significant pain relief was achieved in all patients within 3 days of starting the antibiotic treatment.

All of these patients had large ulcerated tumors surrounded by chronic swelling and erythema prior to onset of the severe pain. All patients had been heavily pretreated with surgery and radiotherapy. Only one of the seven patients had an episode of fever, and only two patients had an increase in wbc count (which was ascribed to corticoid treatment in one of the patients).

Because of the presence of necrosis and ulceration, and because of the location of the tumor, cultures are not very reliable in these patients. This fact probably accounts for the lack of studies on infection in head and neck tumors, even though these patients have been shown to be seriously immunocompromised (4). Some authors have stressed the need for adequate mouth care in patients undergoing radiotherapy (5) or for the local care of open tumors in the mouth or neck (3,6). However, we have found no studies on the incidence of acute infection and its treatment in these patients.

TABLE 1.—Signs of infection, and type and dose of antibiotics and analgesics in the 7 patients

Patient No.	Wbc count, cells/mm³ (% of neutrophils)	Presence of fever	Site of ulceration	Antibiotic treatment	Analgesic treatment before and while on antibiotics	Analgesic treatment after antibiotics
1	Not obtained	No	Skin of the floor of the mouth	Cephalexin (2 g/day orally)	Morphine (440 mg/day orally)	Morphine (240 mg/day orally)
2	Normal (70)	No	Inside the mouth	Penicillin (12 million units/day iv)	Morphine (360 mg/day iv)	Morphine (120 mg/day orally)
3	Normal (65)	No	Skin of the neck	Cephalexin (2 g/day orally)	Morphine (80 mg/day iv)	Morphine (90 mg/day orally)
4	Normal (NA)*	Yes	Skin of the neck	Cephalothin (4 g/day iv)	Morphine (144 mg/day iv)	Morphine (120 mg/day, suppository)
5	11,900† (89)	No	Inside the mouth	Penicillin (12 million units/day iv) + gentamicin (240 mg/day iv)	Morphine (48 mg/day iv)	Morphine (150 mg/day orally)
6	Normal (64)	No	Skin of the neck	Cephalexin (2 g/day orally)	Morphine (77 mg/day iv)	Morphine (180 mg/day orally)
7	16,900 (90)	No	Inside the mouth	Metronidazole‡ (1.5 g/day iv)	Morphine (72 mg/day iv)	Morphine (20 mg/day orally)

*NA = not applicable.
†Patient was receiving corticoids.
‡Patient was allergic to penicillin.

It is well known that pain associated with acute infections disappears rapidly after effective antibiotic treatment. The outcome in these cases suggests that patients had an acute local infection that readily responded to antibiotics. We conclude that acute local infection is probably a frequent event, and should be suspected in patients with head and neck tumors who show a rapidly changing pattern of pain. Fever, leukocytosis, and signs of local infection may be absent, and a therapeutic trial with antibiotics may be necessary in these cases.

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ANNOUNCEMENTS

Sixth Annual Symposium on Fine Needle Aspiration

Budapest, Hungary, August 9–16, 1986

The Department of Pathology at the University of California School of Medicine in San Francisco and the Society of Hungarian Pathologists in cooperation with the California Society of Pathologists are sponsoring the Sixth Annual Symposium on Fine Needle Aspiration, to be held at the Atrium Hyatt Hotel, Budapest, Hungary. This symposium is designed to provide a comprehensive introduction to fine needle aspiration biopsy techniques and interpretive criteria. Tuition includes lectures, extensive syllabus, Kodachrome study set, FNA performance, microscopes, microscopy sessions, and case presentations. The symposium offers ACCME/AMA/CMA Category 1 credits.

For further information, contact: Extended Programs in Medical Education, Rm 569-U, University of California School of Medicine, San Francisco, CA 94143 (telephone: 415-666-4251).

8th Congress of the European Society of Parenteral and Enteral Nutrition

Paris, France, September 14–17, 1986

The 8th Congress of the European Society of Parenteral and Enteral Nutrition will be held in Paris at the Palais des Congres, Porte Maillot, on September 14–17, 1986. The first day, Monday, September 15, will be devoted to an educational session for physicians, pharmacists, dieticians and nurses. The scientific sessions, Tuesday and Wednesday, will consist of two honorary lectures, two symposia, and three workshops. The educational sessions will be presented in French with simultaneous translation to English; the scientific sessions will take place in English, with translation to French.

The Sir David Cuthbertson Lecture will be given by Professor E. Jequier on the "Influence of Nutrient Administration on Energy Expenditure," and the Arvid Wretlind Lecture will be given by Professor D. B. S. Silk on "Towards Optimal Enteral Nutrition."

The programs of the symposia and workshops have been designed to respond to the following questions: control of nitrogen metabolism, the relationship between parenteral nutrition and respiratory function, the importance of preoperative nutrition, digestive adaptation to artificial nutrition, and the present status of home parenteral nutrition in Europe. Parallel sessions will allow for oral communications and poster presentations.

Deadline for submission of abstracts is *April 1, 1986*. Registration fees for the entire congress are as follows: Member (ESPEN, SFNEP, and ASPEN)—prior to June 15, 1986, 950 FF; after June 15, 1986, 1350 FF; Nonmember—prior to June 15, 1986, 1300 FF; after June 15, 1986, 1700 FF. For a detailed breakdown of congress fees other than those already listed, contact: Claude Ricour, *see* address below.

This meeting should meet the criteria for credit hours of the Physician's Recognition Award of the AMA.

For further information, contact: Claude Ricour, Scientific Secretariat, ESPEN 86 149, rue de Sevres, 75743 Paris Cedex 15, France.

IVth Tissue Culture Association Decennial Review—Cell and Tissue Culture International Conference on Molecular Mechanisms in the Regulation of Cell Behavior

Hershey, Pennsylvania, September 22–26, 1986

The IVth Tissue Culture Association Decennial Review—Cell and Tissue Culture International Conference on Molecular Mechanisms in the Regulation of Cell Behavior is scheduled for September

22-26, 1986, at Hershey, Pennsylvania. The program features formal papers, open poster presentations, workshops, and commercial exhibitors. Preregistration ends on *July 22, 1986.*

For further information, contact: Executive Director, Tissue Culture Association, 19110 Montgomery Village Ave, Suite 300, Gaithersburg, MD 20879 (telephone: 301-869-2900).

Urologic Cancer

Boston, Massachusetts, September 22-24, 1986

This intensive, 3-day course will provide an overview of the clinical and pathophysiological basis for the diagnosis and treatment of patients with urologic cancer. This course will emphasize the multidisciplinary approach which constitutes the foundation of contemporary care for patients with urologic cancers. Principles derived from the disciplines of urologic surgery, medical oncology, and radiation therapy will be highlighted and incorporated into a comprehensive consideration of therapeutic practices. While teaching will be primarily provided through lectures, there will be an emphasis on panel discussion of both problem management cases and controversies in urologic cancer. Specifically, definitive lectures and panels highlighting controversies in care will be provided for prostate cancer, bladder cancer, with a special emphasis on newer therapeutic modalities, and testicular cancer. Intensive interaction with the faculty will be provided by question and answer periods, as well as informal lunches attended by both faculty and students. In addition, a comprehensive syllabus will be provided.

Guest Faculty will include Drs. Malcolm A. Bagshaw, John P. Donohue, Lawrence H. Einhorn, and Derek Raghavan. The Harvard/Local faculty includes leaders in urologic cancer from the Dana-Farber Cancer Institute, Brigham and Women's Hospital, Massachusetts General Hospital, Lahey Clinic, University of Massachusetts Medical Center, and Rhode Island Hospital.

Tuition is $390, with a reduced fee of $275 for fellows and residents.

For further information, contact: Harvard Medical School, Department of Continuing Education, Boston, MA 02115 (telephone: 617-732-1525).

Bone and Cancer: International Congress in Hanasaari

Helsinki, Finland, October 9-11, 1986

For further information, contact: European Forum for Orthopaedic Science Congress Bureau, PO Box 4, SF-00661 Helsinki, Finland.

Ninth Annual Bristol-Myers Symposium on Cancer Research

Washington, DC, October 15-16, 1986

The Vincent T. Lombardi Cancer Research Center of Georgetown University School of Medicine is organizing the Ninth Annual Bristol-Myers Symposium on Cancer Research. This year's topic will be "Mechanisms of Drug Resistance in Neoplastic Cells." Sessions include: general considerations of drug resistance; enzymatic basis of drug resistance; multidrug resistance; and the circumvention of resistance.

The annual Bristol-Myers symposium is part of an $8.34 million program of unrestricted grants for cancer research the company has sponsored since 1977 at 17 institutions in the United States, Canada, Europe, and Japan.

For more information, contact: Ms. Lillian Kamal, Administrator, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, 3800 Reservoir Rd, NW, Washington, DC 20007.

Fifth NCI-EORTC Symposium on New Drugs in Cancer Therapy

Amsterdam, The Netherlands, October 22-24, 1986

This symposium will be organized by the European Organization for Research on Treatment of Cancer (EORTC) and by the National Cancer Institute (NCI), National Institutes of Health. The following topics will be discussed: screening and pharmacology, formulation, phase I trials and clinical pharmacology, phase II trials of new cytostatic agents, new analogs, and biological response modifiers.

For further information, contact: Symposium Secretariat, EORTC-New Drug Development Office, Department of Oncology, Free University Hospital, De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands [telephone: (20) 548-5193, 548-5192].

Chemotherapy Foundation Symposium VII—Innovative Cancer Chemotherapy for Tomorrow

New York, New York, November 12–14, 1986

The Sheraton Centre Hotel in New York City will be the location for the Chemotherapy Foundation Symposium VII—Innovative Cancer Chemotherapy for Tomorrow, to be held November 12–14, 1986. Individual sessions will be devoted to postmenopausal breast cancer polychemotherapy, differentiation chemotherapy, chemoimmunotherapy, and new phase II drugs.

The 3-day symposium is being sponsored by the Division of Medical Oncology, Department of Medicine, Department of Neoplastic Diseases, and the Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY).

For further information, contact: Director, The Page and William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029 (telephone: 212-650-6772).

AIDS and the Nervous System

San Francisco, California, December 11–12, 1986

This symposium, located in the St. Francis Hotel and sponsored by the University of California in San Francisco, is designed to present the most recent information on the care of AIDS patients with neurological disease including: overview and neuroepidemiology, clinical syndromes and diagnosis, primary and opportunistic viral infections, non-viral infectious disease, Kaposi's sarcoma and systemic lymphomas, patient care issues, and recent research developments. Ten hours of ACCME/AMA/CMA Category 1 credit may be earned by attending the symposium.

For further information, contact: Extended Programs in Medical Education, Rm 569-U, University of California, San Francisco, CA 94143 (telephone: 415-476-4251).

Third International Conference on Malignant Lymphoma: Current Status and Prospects

Lugano, Switzerland, June 10–13, 1987

The Palazzo dei Congressi is the location for this series of lectures and workshops dealing with the diagnosis and treatment of Hodgkin's and non-Hodgkin's lymphoma in adults and children. Most lectures will be given by invited speakers. The program will include free presentations, workshops, and a poster session. The deadline for the receipt of abstracts is *January 15, 1987.*

For further information, contact: F. Cavalli, MD, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland (telephone: 091-23-62-10).

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Cancer Treatment Symposia: Proceedings of the National Institutes of Health Consensus Development Conference on Limb-Sparing Treatment of Adult Soft Tissue Sarcoms and Osteosarcomas

The International Cancer Information Center of the National Cancer Institute announces the publication of the Proceedings of the National Institutes of Health Consensus Development Conference on Limb-Sparing Treatment of Adult Soft Tissue Sarcomas and Osteosarcomas, which was held December 3-5, 1984.

Amputation of an extremity has been a relatively frequent choice of treatment for both types of sarcoma. However, it appears from clinical evidence reported at this conference that limb-sparing treatment consisting of radiation therapy and/or regional or systemic chemotherapy in conjunction with surgery is feasible and appropriate for a significant proportion of patients with these sarcomas. Experts in the field reported their experience with the management of more than 2000 patients with high-grade extremity sarcomas. Discussion included such issues as preoperative evaluation; extent of surgical resection required; results of this treatment in comparison to amputation; and optimal treatment strategy. A consensus panel drawn from the medical and allied health professions considered the evidence and formulated conclusions related to the issues.

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